LONG TERM FOLLOW UP OF CHILDHOOD CANCER SURVIVORS TO MONITOR LATE EFFECTS OF TREATMENT AT AFTER COMPLETION TREATMENT CLINIC AT CANCER INSTITUTE (WIA) CHENNAI

This dissertation is submitted to

The Tamilnadu Dr MGR Medical University, Chennai in partial fulfillment of the regulations for D.M.(Medical Oncology) Degree Examination of February 2007

CANCER INSTITUTE (W.I.A)

Adyar Chennai-600020

CERTIFICATE

This is to certify that this dissertation on "**Long Term Follow up of Childhood Cancer Survivors to monitor Late Effects of Treatment"** is a bonafide work done by **Dr. Rejiv Rajendranath,** in the Department of Medical Oncology, College of Oncolgical sciences, Adyar, Chennai,, under my overall supervision and guidance, to my satisfaction

Dr.T.G.Sagar, M.D, D.M.
Professor & Head
Department of Medical Oncology
College of Oncological Sciences
Adyar, Chennai-600020

Chennai
Date:

ACKNOWLEDGEMENT

I would like to take this opportunity to express my deep sense of gratitude to my esteemed teacher and guide **Dr. T.G. Sagar, M.D., D.M.,** Professor and Head, Division of Medical Oncology, Cancer Institute (WIA), Adyar, Chennai for his valuable help, guidance and encouragement throughout the course of this work and my post graduate career.

I am ever grateful to **Dr. Anita Chandra, M.D., D.M.,** for her constant encouragement, support and advise during this study.

I thank **Dr. Ganapathhy Ramanan M.D., D.M.,** Associate Professor, Division of Medical Oncology for his valuable comments and suggestions during my post graduate career.

I also thank **Dr. Krishna Reddy M.D., D.M.,** Assistant Professor of Medical Oncology for his support and advise during my post graduate career.

I thank my wife, parents, colleagues and my friends for their constant encouragements and support during this work.

Finally, I would like to express my gratitude to all the childhood cancer survivors who formed the backbone of this study making this a reality.

CONTENTS

INTRODUCTION

An increasing number of childhood cancer survivors have led to a heightened appreciation of the late complications caused by the disease and its treatment. In the USA, 5-year survival for all type of childhood cancers increased from 51% in 1973 to79% in 1997 [1] Incidence of childhood cancer in India is 9 per million [2]. Advances in multimodality therapy have dramatically improved the cure rates of pediatric cancers in the past 2 decades. 5 year survival rates for childhood cancers have also improved in our country [3].

The therapy responsible for this survival can also produce adverse long-term health-related outcomes that manifest months to years after completion of cancer treatment, and are commonly referred to as late effects.

Risk factors for late effects include: [4]

Tumor-related factors

- Direct tissue effects.
- Tumor-induced organ dysfunction.
- Mechanical effects.

Treatment-related factors

- *Radiation therapy:* Total dose and fraction size, organ or tissue volume, and machine energy are the most critical factors.

- *Chemotherapy:* Agent type, single and cumulative dose and schedule may modify risk.

- *Surgery:* Technique and site are relevant.

Host-related factors

- Developmental status.
- Genetic predisposition.
- Inherent tissue sensitivities and capacity for normal tissue repair.
- Function of organs not affected by radiation therapy or chemotherapy.
- Premorbid state.

Late effects include organ dysfunction, second malignant neoplasm, and adverse psychosocial sequelae [5].

Monitoring after childhood cancer should have two main goals:

1) to confirm continued remission and
2) to monitor for late effects of cancer or its therapy.

Although survival rates of childhood cancer have steadily increased in our country there is paucity of data regarding long term follow up of survivors. The purpose of this study was to determine the long term sequale associated with therapy in childhood cancer survivors attending a regional cancer centre in India.

AIM

This study was designed to identify adverse late effects of both cancer and its therapy among childhood cancer survivors.

REVIEW OF LITERATURE

Childhood cancers exhibit greater diversity in terms of anatomical site and histologic type than adult cancers, where carcinomas of the breast, lung and gut predominate. Of all childhood cancers, approximately one third are leukemias and 80% of these are Acute lymphoblastic leukemia (ALL), 25% are brain and spinal tumours, 15% are embryonal tumours, 11% are lymphomas and the remainder is comprised of bone and other rare tumours in western population.[6] In our hospital cancer registry, Cancer Institute, Chennai data from 1998-2002, among pediatric cancers 37% are leukemia, 34% lymphomas and 12% bone and soft tissue sarcoma, eye and brain tumors are 17%.[7]

The last three decades have seen tremendous improvements in survival of children diagnosed with cancer, with the 5-year survival rate approaching 80%. This improvement in survival has resulted in a growing population of childhood cancer survivors.

In 1997, there were an estimated 270,000 survivors of childhood cancer in the US, with 1 in 1000 individuals being a childhood cancer survivor.[2] Demographics of the childhood cancer survivors in the US reveal that while a third of these survivors are still less than 20 years of age, 46% are between 20 and 40 years old and an additional 18% are over 40 years of age [8].

Table-1: 5 year survival rates (%) in childhood cancers from 1962-1996. (Source- National Registry of Childhood Tumours-Scotland) [6]

	1962-66	**1967-71**	**1972-76**	**1977-81**	**1982-86**	**1987-91**	**1992-96**
ALL	4	17	44	56	70	75	81
AML	2	2	7	17	30	47	54
Brain tumours	37	37	43	48	54	57	68
Ewings	25	23	40	34	45	68	61

GCT	55	52	56	74	90	94	96
Hodgkins	39	68	81	89	89	93	94
NHL	17	21	26	45	67	76	78
Neuroblastoma	18	17	19	31	43	41	53
Retinoblastoma	88	86	88	88	89	93	94
RMS	25	23	33	44	58	59	66
Wilms	29	43	62	76	80	82	80
ALL CANCERS	**24**	**29**	**42**	**51**	**62**	**67**	**73**

Abbreviation

ALL- Acute Lymphoblastic leukemia, AML- Acute myeloid leukemia,GCT- germ cell tumours ,NHL – Non Hodgkin lymphoma , RMS - Rhabdomyosarcoma

Large epidemiological studies have analyzed the subsequent mortality and its causes in children and adolescents who survived five years from the diagnosis of cancer. Two studies found that 5-year survivors of childhood cancer have a standardized mortality ratio (SMR) of 11 (ie an 11 fold increased risk of death in subsequent years when compared with age and sex specific expected rates for the general population[9] . A North American study comprising of 20,227 5 year childhood cancer survivors diagnosed between 1970 and 1986 showed a significantly higher SMR of 18 in female survivors, individuals diagnosed with cancer before the age of 5 years (SMR=14) and those with an initial diagnosis of leukemia (SMR=15.5) and central nervous system tumour (SMR=15.7). The leading cause of death among 5 year survivors was recurrence of the original cancer with a statistically significant excess mortality rate seen due to subsequent malignancies (SMR=19.4) as well as cardiac (SMR=8.2), pulmonary (SMR=9.2) and other causes (SMR=3.3). There was no excess mortality from external causes like road traffic accidents. These studies provide a resource for understanding how mortality may be reduced further, and how modifications of current therapy may reduce treatment related mortality in the future [9].

Curry et al in their childhood survivor study noted that 61 % of survivors have one or more chronic medical problems and require multidisciplinary care [10] and about one third will experience a late effect that is severe or life threatening.

Common late effects based on treatment modality are as described in the following tables [11].

Table 2 Late Effects of Chemotherapy

Organ/ Tissue	Predisposing drug(s)	Late Effect
Brain	Methotrexate, Cytarabine (high dose, intrathecal)	Leukoencephalopathy, neurocognitve dysfunction, seizures
Nerves	Cisplatin, Vincristine,Vinblastine	Hearing loss Peripheral neuropathy, foot drop
Heart	Anthracyclines Cyclophosphamide (high dose)	Cardiomyopathy Cardiac failure. arrythmias
Lungs	Bleomycin, BCNU,Cyclophosphamide	Pulmonary fibrosis
Liver	Methotrexate. BCNU	Hepatitis, Hepatic fibrosis
Kidney	Cisplatin, Ifosphamide high dose methotrexate, Nitosureas	Renaltubular dysfunction, Hypomagnesemia Reduced renal filtration, Renal failure (rare)
Bladder	Ifosphamide, Cyclophosphamide	Haemorrhagic cystitis, Bladder fibrosis, Carcinoma bladder
Testes and Ovaries	Alkylating agents (Chlorambucil, Cyclophosphamide, procarbazine, BCNU, CCNU)	**Females**: Low estrogen levels, ovarian failure, Infertility, early menopause **Males:**azoospermia, infertility, Hypogonadism
Bone marrow	Alkylating agents, etoposide, tenoposide	Myelodysplasia, t-AML
Bones	Corticosteroids, methotrexate	Osteoporosis, avascular necrosis
Skin	Bleomycin, dactinomycin	Hyperpigmentation

Table 3 Late effects of Radiation Therapy

Field	Late effects
All tissues	Second malignancies, skin fibrosis
Cranial	Neurocognitive deficits, endocrinopathies, abnormal tooth development, dental caries, infertility, cataract
Spinal	thyroid dysfunction, kyphoscoliosis, myelitis
Head and neck	Dental caries, thyroid dysfunction, hearing loss, cataracts, osteoradionecrosis, maxillary or mandibular hypoplasia, xerostomia
Orbit	Cataract, corneal ulcer, keratitis, orbital hypoplasia, glaucoma, blepharitis
Mediastinum, pulmonary, Mantle	Cardiomyopathy, pericarditis, coronary and valvular heart disease, arrythmias, pulmonary fibrosis, breast hypoplasia, esophageal stricture
Abdominal	Hepatic fibrosis, esophageal varices, renal damage, renal artery stenosis, scoliosis, intestinal fibrosis, malabsorption
Testicular	Leydigs cell failure.infertility
Pelvic	Gonadal failure, marrow hypoplasia, bladder and ureteral fibrosis, urethral strictures, vaginal fibrosis, hemorrhagic cystitis
Extremity	Growth discrepancy, pathological fractures, muscular hypoplasia, necrosis
Total Body Irradiation	Growth failure, hypothyroidism, gonadal failure, cataracts

Table 4 Late Effects of Surgery

Surgery	Late Effect
Limb salvage	Pathological fractures, limited movements, graft infection, loosening of prosthesis
Amputation	Prosthesis and stump complications, cosmetic deformity, psychosocial effects
Laparotomy	Fistulas, bowel obstruction
Nephrectomy	Hypertension and renal dysfunction
Orchidectomy, Oopherectomy	Gonadal failure
Splenectomy	Impaired immune function, overwhelming sepsis (encapsulated bacteria)
Thyroidectomy	Hypothyroidism
Enucleation	Prosthesis complications and blindness

Common Late Effects of Childhood Cancer by Body System

Central Nervous System

Neurocognitive

Neurocognitive late effects most commonly follow treatment of malignancies that require central nervous system (CNS)-directed therapies, such as cranial radiation or intraventricular/intrathecal (IT) chemotherapy; thus, children with CNS tumors, head and neck sarcomas, and acute lymphoblastic leukemia (ALL) are most commonly affected [12]. Deficits occur in a variety of areas that include the following

General intelligence.

- Age-appropriate developmental progress.
- Academic achievement (especially in reading, language, and mathematics).
- Visual and perceptual motor skills.

- Nonverbal and verbal memory.
- Receptive and expressive language and attention.

For ALL, studies again show significant neurocognitive impairment [13]. Even when combined with intrathecal chemotherapy, reduction in the cranial radiation dose has resulted in less neurocognitive impairment [14]. Deficits in fine motor skills, visual-spatial abilities, verbal and nonverbal memory, psychomotor speed and shifting of attention, auditory perception, word fluency, contingency naming, and the ability to follow directions have all been reported [15].

Copeland et al. showed combined treatment is associated with more severe cognitive and academic deficits than CNS chemotherapy alone [16]. In this and the other studies cited, children were treated with high dose (2400 cGy) radiotherapy. There is some evidence that low dose cranial irradiation (i.e., 1800 cGy) has a milder effect on cognitive functioning than higher doses .Irradiation-or chemotherapy-induced destruction in normal white matter partially explains intellectual and academic achievement deficits [17]. Combined-therapy participants had significantly smaller amplitude and slower response of the P-300 (a brain-evoked potential associated with attention) The function of myelin is to increase axonal conduction velocity, the results of this study suggest that the effect of CRT impeded neuronal transmission speed. These result in a slowing and disorganization of cognitive processing that was manifested in neurocognitive deficits [18]. Children with leukemia spend considerable time in the hospital, miss significant amounts of school, tire more easily than healthy children, and are restricted in the more active aspects of learning. These factors have been related to lowered performance on IQ tests, particularly on Weschlers Intelligence Scale – Revised(WISC-R) subtests with a strong educational component [19].

Systemic methotrexate in high doses and combined with radiation therapy can lead to a well-described leukoencephalopathy, in which severe neurocognitive deficits are obvious. The deleterious effects of systemic methotrexate, especially at doses above 1 g/m^2 may be no

different or worse than those of 18 Gy of cranial radiation therapy [20] At lower methotrexate doses, there does not appear to be a consistent pattern of neurocognitive deficits [21]. One long-term study of infants who received high-dose systemic methotrexate combined with intrathecal cytarabine and methotrexate for CNS leukemia prophylaxis and who were tested 3 to 9 years posttreatment showed that cognitive function was in the average range.[22]

Chemotherapy alone for ALL may result in cognitive dysfunction. One study examined 48 children treated for leukemia without cranial radiation therapy and found impairment in tasks of higher-order cognitive functioning and learning disabilities in the area of mathematics. [20] Another study showed that children, particularly females, treated with systemic and IT methotrexate for CNS leukemia prophylaxis showed impairment of verbal memory and coding. [23].

Table 5 CNS late effects

Late Effect	Causative Treatment	Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
Neurocognitive deficit	**Chemotherapy:** High-dose IV methotrexate, IT methotrexate	Difficulty with: reading, language, verbal and nonverbal memory, arithmetic, receptive and expressive language, attention deficit, decreased IQ,	Neurocognitive testing: psycho-educational, neuropsychologic	Psychoeducation assistance
	Radiation: >18 Gy			
Leuko-encephalopathy	**Chemotherapy:** methotrexate: IT or IV, IT cytarabine	Seizures, neurologic impairment, compare with premorbid status	Computed tomography (CT)/ magnetic resonance imaging (MRI) scan baseline and symptoms	Symptom management: muscle relaxants, anticonvulsants, physical therapy, occupational therapy

Late Effect	Causative Treatment	Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
	Radiation: >18 Gy (with methotrexate)			
Focal necrosis	**Chemotherapy:** methotrexate: IT or high-dose IV carmustine (BCNU), cisplatin	Headaches, nausea, seizures, papilledema, hemiparesis/other focal findings, speech, learning, and memory deficits	CT/MRI scan baseline, as needed for symptoms, positron emission tomography or single photon emission computed tomography scan	Steroid therapy, debulking of necrotic tissue
	Radiation: >50 Gy (especially with >2 Gy daily fraction)			
	Surgery: Resection of tumor			
Vision loss	**Radiation:** >50 Gy (optic nerve chiasma)	Progressive visual loss	Ophthalmic evaluation, visual-evoked response	Visual aids
Ototoxicity	**Chemotherapy:** CDDP, carboplatin	Abnormal speech development, hearing	Audiogram baseline	Speech therapy, hearing aid
Myelitis	**Radiation:** >45-50 Gy	Paresis, spasticity, altered sensation, loss of sphincter control	MRI	Steroids, physical therapy, occupational therapy
	Surgery: Spinal cord surgery			

TABLE-6 Neurocognitive outcome in survivors of pediatric cancer [23]

Psychosocial

Many childhood cancer survivors have adverse quality of life or other adverse psychologic outcomes. Incorporation of psychological screening into clinical visits for childhood cancer survivors may be valuable; however, limiting such evaluations to those returning to long-term follow-up clinics may result in a biased subsample of those with more difficulties, and precise prevalence rates may be difficult to establish. A review of behavioral, emotional, and social adjustment among survivors of childhood brain tumors illustrates this point, in whom rates of psychological maladjustment range from 25% to 93% [24].

Studies in the early 1990s described childhood cancer survivors as generally well adjusted, though a subset had psychological difficulties that resulted in functional impairment [25]. Further in-depth analyses have led to the description of posttraumatic stress disorder (PTSD) in some childhood cancer survivors and their mothers. The core features of PTSD include:[26] experiencing an event perceived as life threatening, with an accompanying reaction of intense fear, horror, or helplessness, persistent re-experiencing of the event, avoiding things, events, or people surrounding the event or decreased responsiveness to same, increased sleep disturbance, irritability, hypervigilance, and difficulty in concentrating.

Because avoidance of places and persons associated with the cancer is part of PTSD, the syndrome may interfere with obtaining appropriate health care. Those with PTSD perceived greater current threats to their lives or the lives of their children. Other risk factors include poor family functioning, decreased social support, and noncancer stressors. One study of 78 young adult survivors of childhood cancer found 20.5% met the criteria for PTSD. In contrast, only 4.5% of younger children met the criteria for the syndrome [27].

In a study of 101 adult cancer survivors of childhood cancer, psychologic screening was

performed at the survivorship clinic at the Dana Farber Cancer Institute. On the Symptom Checklist 32 subjects had a positive screen (indicating psychological distress), and 14 subjects reported at least 1 suicidal symptom. Risk factors for psychological distress included subjects' dissatisfaction with physical appearance, poor physical health, and treatment with cranial radiation. In this study, the instrument was shown to be feasible in the setting of a clinic visit because the psychological screening was completed in less than 30 minutes [28]. In a recent study reported from India behaviour and adjustment problems were noted among 20% of childhood cancer survivors and depression was noted among 27% of subjects [29].

Special Senses

Hearing

Hearing loss is a common late effect of survivors of CNS cancers and cancers of the head and neck who received high doses of radiation therapy and platinum chemotherapy. Hearing loss in the speech range (0.5 kHz to 3 kHz), which may compromise language reception and expression, is reported with cumulative doses of cisplatin greater than 360mg/m^2, and 25% prevalence of hearing loss is reported with doses greater than 720 mg/m^2. Fifty percent of children treated with cisplatin doses greater than 450 mg/m^2 have sensorineural hearing loss (SNHL) in the high frequencies (6 kHz to 8 kHz). Younger age at time of administration increases risk [30]. Radiation therapy can result in cochlear damage, with SNHL occurring in about 25% of patients treated with doses approaching 60 Gy [31]. The sequence of chemoradiotherapy appears to influence risk. Risk and severity of ototoxicity are greater when cisplatin is administered after cranial radiation.[32]

Optic and Orbital

Orbital complications are common following radiation therapy for childhood head and

neck sarcomas, CNS tumors, and retinoblastoma and as part of total-body irradiation (TBI).

For survivors of retinoblastoma, a small orbital volume may result from either enucleation or radiation therapy. Age younger than 1 year may increase risk, but this is not consistent across studies. Treatment for tumors located near the macula and fovea increase risk of complications leading to visual loss [32].

Survivors of orbital rhabdomyosarcoma are at risk of dry eye, cataract, orbital hypoplasia, ptosis, retinopathy, keratoconjunctivitis, optic neuropathy, lid epithelioma, and impairment of vision following radiation therapy doses of 30 Gy to 65 Gy. The higher dose ranges (>50 Gy) are associated with lid epitheliomas, keratoconjunctivitis, lacrimal duct atrophy, and severe dry eye. Retinitis and optic neuropathy may also result from doses of 50 Gy to 65 GyCataracts are reported following lower doses of 10 Gy to 18 Gy [33].

Patients treated with TBI are also at increased risk of cataracts. Risk ranges from approximately 10% to 60% at 10 years posttreatment, depending on the total dose and fractionation, with a shorter latency period and more severe cataracts noted after single fraction and higher dose or dose-rate TBI. Corticosteroids and graft-versus-host-disease (GVHD) may further increase risk [34].

Table 7. Eye Late Effects

Late Effect	Causative Treatment	Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
Lacrimal glands: decreased tear production	**Radiation:** >50 Gy	Dry, irritated red eye, foreign-body sensation, positive fluorescein staining	Penlight/slit lamp exam, fluorescein staining	Tear replacement, occlude lacrimal puncta, education regarding avoiding rubbing lids when puncta plug is intact
Cornea: ulceration	**Radiation:** >45 Gy	Pain, foreign-body sensation, decreased visual acuity, photosensitivity	Slit lamp/penlight exam, fluorescein staining	Tear replacement, antibiotics, soft bandages, soft contact lens, surgery, ophthalmology
Neovascularization	**Radiation:** >50 Gy	Increased tearing, increased vessels surrounding edge of cornea	Slit lamp exam	Tear replacement, antibiotics, soft bandages, soft contact lens, surgery,
Lens: cataract	**Chemotherapy:** Steroids)	Decreased visual acuity, opaque lens	Direct ophthalmoscopic exam, decreased red reflex, slit lamp/penlight exam: opaque lens	Prevention by shielding during treatment, surgical removal, educate regarding UV protection
	Radiation: >10-15 Gy (fractionated)			
Secondary glaucoma	—	Eye pain, headache, nausea/vomiting, decreased peripheral vision, increased intraocular pressure	Measure ocular pressure	Beta blocker drops, atropine, acetazolamide (Diamox)
Atrophy	**Radiation:** >50 Gy	Decreased iris stroma at pupillary margin	Slit lamp/penlight exam	Photocoagulation
Hemorrhage	**Radiation:** >50 Gy	—	Visual acuity,, fundus photography	Steroids, photocoagulation,
Optic neuropathy	**Radiation:** >50 Gy	Pale optic disc, abnormal pupillary responses	Visual evaluation	Visual aids

Digestive System

Dental

Both chemotherapy and radiation therapy can cause multiple cosmetic and functional abnormalities of dentition, most predominantly in children treated before age 3 years who have not yet developed deciduous dentition.

Doses of 20 Gy to 40 Gy can cause root shortening or abnormal curvature, dwarfism, and hypocalcification [35]. More than 85% of survivors of head and neck rhabdomyosarcoma who receive radiation doses greater than 40 Gy may have significant dental abnormalities, including mandibular or maxillary hypoplasia, increased caries, hypodontia, microdontia, root stunting, and xerostomia. Chemotherapy for the treatment of leukemia can cause shortening and thinning of the premolar roots as well as enamel abnormalities [36]. Salivary gland irradiation incidental to treatment of head and neck malignancies or Hodgkin's lymphoma causes a qualitative and quantitative change in salivary flow, which can be reversible after doses of less than 40 Gy but may be irreversible after higher doses. Dental caries are the most problematic consequence. The use of topical fluoride can dramatically reduce the frequency of caries, and saliva substitutes and sialagogues can ameliorate sequelae such as xerostomia [37].

Hepatic

Most chemotherapy agents employed in childhood cancer therapy can have acute hepatotoxic effects. In the modern era, long-term hepatic effects following chemotherapy alone are uncommon Cumulative dose, volume of liver irradiated, and additional treatment with chemotherapy are important risk factors for hepatic fibrosis. Radiation hepatopathy can occur with doses of 30 Gy to 40 Gy to the entire liver [38].

Patients who received blood transfusions before 1992 are at increased risk of developing hepatitis C infection. Those infected may then progress to chronic active hepatitis and cirrhosis, and have an increased risk of developing hepatocellular carcinoma. The incidence risks range widely from 6% to 49% across studies, but may likely be in the 20% to 25% range overall [39]. Therefore, all children who received blood transfusions before 1992 should be screened for hepatitis C virus. Those found to be positive should be referred to gastroenterologists for consideration of therapy in ongoing studies.

Digestive Tract

Late radiation injury to the digestive tract is attributable to vascular injury. Necrosis, ulceration, stenosis or perforation can occur and are characterized by malabsorption, pain, and recurrent episodes of bowel obstruction, as well as perforation and infection [40]. Doses greater than 40 Gy are required to cause bowel obstruction or chronic enterocolitis.Sensitizing chemotherapeutic agents such as dactinomycin or anthracyclines can increase this risk [41].

Table 8 Gastrointestinal (GI) Late Effects

Late Effects	Causative Treatment	Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
Enteritis	**Chemotherapy:** actinomycin D and doxorubicin (enhance radiation therapy effect)	Abdominal pain, diarrhea, decreased stool bulk, emesis, weight loss, poor linear growth	Height and weight every year, stool guaiac every year, complete blood count (CBC) with mean corpuscle volume (MCV) every year, total protein & albumin every 3-5 years (absorption tests, vitamin B_{12} level, and contrast studies)	Dietary management, refer to gastroenterologist
	Radiation: >40 Gy			
	Surgery: Abdominal surgery enhances RT effect			
Adhesions	**Radiation:** Radiation enhances effect	Abdominal pain, bilious vomiting, hyperactive bowel sounds	Abdominal radiograph	Nothing by mouth, gastric suction, adhesion lysis
	Surgery: Laparotomy			
Fibrosis: esophagus (stricture)	**Chemotherapy:** actinomycin D and doxorubicin	Weight loss, dysphagia, poor linear growth	Height and weight every year, CBC every year, (barium swallow/endoscopy as needed)	Esophageal dilation, antireflux surgery
	Radiation: >40-50 Gy			
	Surgery: Abdominal surgery			
Fibrosis: small intestines	**Radiation:** >40 Gy	Diarrhea, weight loss, obstruction, abdominal pain, constipation	Height and weight every year, CBC with MCV every year, serum protein & albumin every 3-5 years (upper GI, small bowel biopsy)	High-fiber diet, decompression, resection, balloon dilation
	Surgery: Abdominal surgery			

Late Effects	Causative Treatment	Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
Fibrosis: large intestine, colon	**Radiation:** >40 Gy	Abdominal colic, rectal pain, constipation, melena, weight loss, obstruction	Height and weight every year, rectal exam, stool guaiac every year, lower GI, colonoscopy, sigmoidoscopy	Stool softeners, high-fiber diet
	Surgery- Abdominal surgery			

Immune System

Spleen

Splenectomy increases risk of life-threatening invasive bacterial infection [42]. It is no longer standard practice to perform a staging laparotomy for pediatric Hodgkin's lymphoma. Therefore, the previously described long-term complications, related to both surgery and altered immune function, should no longer be an issue for most survivors of childhood cancer [43]. Children may be rendered asplenic by radiation therapy to the spleen in doses greater than 30 Gy, however, given as involved-field irradiation or as part of nodal irradiation [44].

For patients with surgical or functional asplenia, prophylactic antibiotics (generally penicillin) are recommended as daily lifelong treatment. No randomized studies that address the benefit of antibiotics have been conducted in a pediatric oncology population; thus, these recommendations are based on any pediatric population with asplenia [45]. As a result, some patients, over time, discontinue use of antibiotics. In these cases, antibiotics—generally penicillin—should be taken at the first onset of febrile illness if the patient is not on daily prophylaxis. Medical care should be sought promptly for fevers higher than 38.5° C. Patients should receive antibiotic prophylaxis for dental work and should be immunized against *meningococcus*, *hemophilus influenzae* type B, and *Streptococcus pneumoniae[42]*.

Circulatory System

Cardiovascular

Childhood cancer survivors exposed to anthracyclines (doxorubicin, daunorubicin, idarubicin, epirubicin, mitoxantrone) or thoracic radiation therapy are at risk for long-term cardiac toxicity. The risks to the heart are related to cumulative anthracycline dose, method of administration, amount of radiation delivered to different depths of the heart, volume and specific areas of the heart irradiated, total and fractional irradiation dose, age at exposure, latency period, and gender.

The effects of thoracic radiation therapy are difficult to separate from those of anthracyclines because few children undergo thoracic radiation therapy without the use of anthracyclines. The pathogenesis of injury differs, however, with radiation primarily affecting the fine vasculature of the heart and anthracyclines directly damaging myocytes.[] Late effects of radiation to the heart include delayed pericarditis ,pancarditis, which includes pericardial and myocardial fibrosis, with or without endocardial fibroelastosis, myopathy. coronary artery disease (CAD), functional valve injury and conduction defects [46].

In a study of 635 patients treated for childhood Hodgkin's lymphoma, the actuarial risk of pericarditis requiring pericardiectomy was 4% at 17 years posttreatment (occurring only in children treated with higher radiation doses). Only 12 patients died of cardiac disease, including 7 deaths from acute myocardial infarction; however, these deaths occurred only in children treated with 42 Gy to 45 Gy(N121) Among children treated with 15 Gy to 26 Gy, none developed radiation-associated cardiac problems [47]. Increased risk of doxorubicin-related cardiomyopathy is associated with female sex, cumulative doses greater than 200 mg/m^2 to 300 mg/m^2, younger age at time of exposure, and increased time from exposure [48]. Route of

administration of doxorubicin may influence risk of cardiomyopathy Earlier studies in adults have shown decreased cardiotoxicity with prolonged infusion; [49], but in a pediatric population one study looked at the effect of continuous (48-hour) versus bolus (1-hour) infusions of doxorubicin in 121 children who received a cumulative dose of 360 mg/m^2 for treatment of ALL and found no difference in the degree or spectrum of cardiotoxicity in the 2 groups [50].

Prevention or amelioration of anthracycline-induced cardiomyopathy is clearly important because the continued use of anthracyclines is required in cancer therapy. Dexrazoxane (DZR) is a bisdioxopiperazine compound that readily enters cells and is subsequently hydrolyzed to form a chelating agent. Evidence supports its capacity to mitigate cardiac toxicity in patients treated with anthracyclines [51].

Rhythm disturbances are also reported after doxorubicin exposure. One study looked at electrocardiograms (ECGs) in 52 long-term survivors of childhood cancer who had been treated with anthracyclines. Prolongation of corrected QT interval (QTc) of more than 0.43 was noted in 6 of 22 patients who had received cumulative anthracycline doses greater than 300 mg/ m^2, as compared with 0 of 15 patients who had received lower anthracycline doses [52].

Table 9-Cardiac Late Effects

Late Effects	Causative Treatment	Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
Cardiomyopathy	**Chemotherapy:** anthracycline >300 mg/m^2, >200 mg/m^2 and radiation therapy to mediastinum, high-dose cyclophosphamide, (bone marrow transplant [BMT]) (possibly ifosfamide)	Fatigue, cough, dyspnea on exertion, peripheral edema, hypertension, tachypnea/rales, tachycardia, cardiomegaly (S3/S4), hepatomegaly, syncope, palpitations, arrhythmias	ECG, echocardiogram/ radionuclear angiography and chest x-ray baselines, every 2-5 years (depending on risk factors), Holter monitor and exercise testing baseline, as needed for symptoms and after high cumulative anthracycline dose (>300 mg/m^2)	Diuretics, digoxin, afterload reduction, antiarrhythmics, cardiac transplant, education regarding risks of: isometric exercises, alcohol consumption, drug use, smoking, pregnancy, anesthesia
	Radiation: >35 Gy			
	Chemotherapy and Radiation: >25 Gy and anthracyclines			
Valvular damage (mitral/tricuspid aortic)	**Radiation:** >40 Gy	Weakness, cough, dyspnea on exertion, new murmur, pulsating liver	Echocardiogram and chest x-ray (baseline), every 3-5 years then as needed for symptoms	Penicillin prophylaxis for surgery/dental procedures
Pericardial damage	**Radiation:** >35 Gy	Fatigue, dyspnea on exertion, chest pain, cyanosis, ascites, peripheral edema, hypotension, friction rub, muffled heart sounds, venous distension, pulsus paradoxus	ECG (ST-T changes, decreased voltage), echocardiogram, chest x-ray baseline, every 3-5 years	Pericardial stripping
Coronary artery disease	**Radiation:** >30 Gy	Chest pain on exertion (radiates to arm/neck), dyspnea, diaphoresis, pallor, hypotension, arrhythmias	ECG every 3 years, stress test (consider thallium scintigraphy) baseline, every 3-5 years or as needed for symptoms	Diuretics, cardiac medications, low-sodium, low-fat diet, conditioning regimens

A number of studies have examined cardiac function after radiation therapy and anthracycline exposure using cardiopulmonary exercise stress tests and have found abnormalities in exercise endurance, cardiac output, aerobic capacity, echocardiography during exercise testing, and ectopic rhythms [53].

Respiratory System

Pulmonary

Pulmonary fibrotic disease is seen as a late complication of radiation therapyChanges in lung function have been reported in children treated with whole-lung radiation therapy for metastatic Wilms' tumor. A dose of 12 Gy to 14 Gy reduced total lung capacity and vital capacity to about 70% of predicted values,] Administration of bleomycin alone can produce pulmonary toxicity and, when combined with radiation therapy, can heighten radiation reactionsThe development of bleomycin-associated pulmonary fibrosis with permanent restrictive disease is dose dependent, usually occurring at doses greater than 200 U/m^2 to 400 U/m^2, higher than those used in pediatric malignancies [54]. A study evaluated serial pulmonary function in children treated with COP (cyclophosphamide, vincristine, and prednisone)/ABVD and mantle radiation therapy and found 65% to 73% to have only mildly decreased or normal diffusing capacity [55]. One other study reviewed pulmonary toxicity in survivors of childhood ALL, Hodgkin's lymphoma, and non-Hodgkin's lymphoma (NHL) and found some abnormalities as measured by pulmonary function testing [56].

Bronchiolitis obliterans with or without organizing pneumonia, diffuse alveolar damage, and interstitial pneumonia may occur as a component of this syndrome, generally between 6 and 12 months posttransplant. Cough, dyspnea, or wheezing may occur with either normal chest x-ray or diffuse/patchy infiltrates; however, most patients are symptom free [57].

An analysis of self-reported pulmonary complications of 12,390 survivors of common childhood malignancies has been reported by the CCSS. This cohort includes children treated with both conventional and myeloablative therapies. Compared with siblings, survivors had an increased relative risk (RR) of lung fibrosis, recurrent pneumonia, chronic cough, pleurisy, use of supplemental oxygen therapy, abnormal chest wall, exercise-induced shortness of breath and bronchitis, with RRs ranging from 1.2 to 13.0 (highest for lung fibrosis and lowest for bronchitis). The 25-year cumulative incidence of lung fibrosis was 5% for those who received chest radiation therapy and less than 1% for those who received pulmonary toxic chemotherapy [58].

Urinary System

Renal

Cisplatin at doses greater than 200 mg/m^2 can result in glomerular or tubular injury and renal insufficiency. Other nephrotoxic agents such as aminoglycosides, amphotericin, and ifosfamide may further increase risk. Ifosfamide can also cause glomerular and tubular toxicity, with renal tubular acidosis, and Fanconi's syndrome. Doses greater than 60 g/m^2 to 100 g/m^2, age younger than 5 years at time of treatment, and combination with cisplatin and carboplatin increase risk [59].

Radiation nephropathy is dose-related. Doses greater than 25 Gy to both kidneys can cause renal failure at delayed intervals of more than 6 months [60]. One study examined the spectrum of renal failure in 55 patients among the 5,823 patients treated for Wilms' tumor. The incidence of renal failure at 16 years postdiagnosis was 0.6% for patients with unilateral disease and 13% for patients with bilateral disease. The most common etiologies of renal failure were bilateral nephrectomy for persistent or recurrent tumor, progressive tumor in the

remaining kidney without nephrectomy, Denys-Drash syndrome (DDS), and radiation nephritis [61]. In another study from the National Wilms' Tumor Group of children treated from 1969 to 1995, 58 of 5,976 developed renal failure with a median follow-up of 11 years. Patients with bilateral disease and unilateral disease had a 20-year renal failure incidence of 5.5% and 1.0%, respectively.

In the setting of HSCT, fewer than 15% of children will develop chronic renal insufficiency or hypertension; the risk is related to the nephrotoxic agents used and the TBI-fractionation scheme and interfraction interval [57].

Table 10 Kidney and Bladder Late Effects

Late Effects	Causative Treatment	Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
Glomerular dysfunction	**Chemotherapy:** cisplatin, carboplatin	Asymptomatic or fatigue, poor linear growth, anemia, oliguria	Annual: blood pressure, height, weight, hemoglobin/ hematocrit, urinalysis, creatinine, BUN; creatinine clearance baseline and every 3 years	Low-protein diet, dialysis, renal transplant
Tubular dysfunction	**Chemotherapy:** cisplatin, carboplatin, ifosfamide	Seizures (↓magnesium [Mg]), weakness (↓phosphate [PO4]), glycosuria, poor linear growth	Annual: blood pressure, height, weight, hemoglobin/ hematocrit, urinalysis, creatinine, BUN; creatinine clearance baseline and every 3 years and Mg, PO4 (24-hour urine for calcium, PO4)	Mg supplement, PO4 supplement
Bladder: fibrosis or hypoplasia (reduced bladder capacity)	**Chemotherapy:** cyclophosphamide, ifosfamide	Urgency, frequency, dysuria, incontinence (nocturia), pelvic hypoplasia	Urinalysis every year (cystoscopy, intravenous pyelogram/ ultrasound [US] : volumetrics)	Exercises to increase bladder capacity, surgical referral
	Radiation: >30 Gy prepubertal, >50 Gy postpubertal			
Hemorrhagic cystitis	**Chemotherapy:** cyclophosphamide, ifosfamide	Hematuria, frequency, urgency, dysuria, bladder tenderness	Urinalysis every year to rule out urinary tract infection (UTI), renal calculi (cystoscopy if hematuria on 2 exams)	Transfusion, antispasmodics, formalin, counsel regarding risk of bladder cancer
	Radiation: (Radiation enhances chemotherapy effect)			

Thyroid Gland

Thyroid dysfunction, manifested by primary hypothyroidism, hyperthyroidism, goiter, or nodules, is a common delayed effect of radiation therapy fields that include the thyroid gland incidental to treating Hodgkin's lymphoma, brain tumors, head and neck sarcomas, and ALL. Of children treated with radiation therapy, most develop hypothyroidism within the first 2 to 5 years posttreatment, but new cases can occur later. Reports of thyroid dysfunction differ depending on the dose of radiation, the length of follow-up, and the biochemical criteria utilized to make the diagnosis [62].

In a study of 1,677 children and adults with Hodgkin's lymphoma who were treated with radiation therapy between 1961 and 1989, the actuarial risk at 26 years posttreatment for overt or subclinical hypothyroidism was 47%, with a peak incidence at 2-3 years posttreatment [63]. In a study of Hodgkin's lymphoma patients treated between 1962 and 1979, hypothyroidism occurred in 4 of 24 patients who received mantle doses less than 26 Gy but in 74 of 95 patients who received greater than 26 Gy. The peak incidence occurred at 3 to 5 years posttreatment, with a median of 4.6 years [64].

Table 11 Thyroid Late Effects

Late Effects	Causative Treatment	Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
Overt hypothyroidism (elevated TSH, decreased T4)	**Radiation:** >20 Gy to the neck, cervical spine	Hoarseness, fatigue, weight gain, dry skin, cold intolerance, dry brittle hair, alopecia, constipation, lethargy, poor linear growth, menstrual irregularities, pubertal delay, bradycardia, hypotension	Free T4, TSH annually up to 10 years postradiation or if symptomatic, plot on growth chart	Refer to endocrinologist, thyroxine replacement, anticipatory guidance regarding symptoms of hyperthyroidism / hypothyroidism
	Radiation: >7.5 Gy TBI			
	Surgery: Partial or complete thyroidectomy			
Compensated hypothyroidism (elevated TSH, normal T4)	Same as overt hypothyroidism with regard to radiation and surgery	Asymptomatic	Free T4, TSH annually up to 10 years postradiation or if symptomatic, plot on growth chart	Refer to endocrinologist, thyroxine to suppress gland activity
Thyroid nodules	Any dose radiation	Hoarseness, fatigue, weight gain, dry skin, cold intolerance, dry brittle hair, alopecia, constipation, lethargy, poor linear growth, menstrual irregularities, pubertal delay, bradycardia, hypotension	Free T4, TSH annually up to 10 years postradiation or if symptomatic, plot on growth chart, physical exam; ultrasound for technetium^{99}m scan baseline and then as needed for symptoms	Refer to endocrinologist, thyroid scan, biopsy/resection
Hyperthyroidism decreased TSH, elevated T4	Same as overt hypothyroidism with regard to radiation	Nervousness, tremors, heat intolerance, weight loss, insomnia, increased appetite, diarrhea, moist skin, tachycardia, exophthalmus, goiter	Free T4, TSH annually up to 10 years postradiation or if symptomatic, plot on growth chart physical exam; ultrasound for technetium^{99}m scan baseline and then as needed for symptoms, triiodothyronine (T3), antithyroglobulin, antimicrosomal antibody baseline, then as needed.	Refer to endocrinologist, propylthiouracil (PTU), propanol ^{131}I, thyroidectomy

Neuroendocrine System

Other endocrine abnormalities can occur after cranial irradiation, including growth hormone (GH) deficiency, delayed or precocious puberty, and hypopituitarism. Hypothalamic dysfunction is most common, though pituitary insufficiency may occur [65]. Approximately 60% to 80% of irradiated pediatric brain tumor patients who have received doses greater than 30 Gy will have impaired serum GH response to provocative stimulation, usually within 5 years of treatment. The dose-response relationship has a threshold of 18 Gy to 20 Gy; the higher the radiation dose, the earlier the GH deficiency will occur after treatment [66].

Children treated with CNS irradiation for leukemia are also at increased risk of GH deficiency. One study evaluated 127 patients with ALL treated with 24 Gy, 18 Gy, or no cranial irradiation. The change in height, compared with population norms expressed as the standard deviation score (SDS), was significant for all 3 groups with a dose-response of -0.49 ± 0.14 for the no radiation therapy group, -0.65 ± 0.15 for the 18 Gy radiation therapy group, and -1.38 ± 0.16 for the 24 Gy group [67] Another study found similar results in 118 ALL survivors treated with 24 Gy cranial irradiation, in which 74% had SDS score of ≥-1 and the remainder ≥-2.[68] Pubertal growth can be adversely affected by cranial radiation. Doses greater than 50 Gy may result in gonadotrophin deficiency, while doses in the range of 18 Gy to 47 Gy can result in precocious puberty. Precocious puberty has been reported in some children receiving cranial irradiation, mostly in girls who receive doses greater than 24 Gy cranial radiation. Earlier puberty and earlier peak height velocity, however, are seen in girls treated with 18 Gy cranial radiation [69]. Another study showed that the age of pubertal onset is positively correlated with the age at the time of cranial irradiation. The impact of early puberty in a child with radiation-associated GH deficiency is significant, and timing of GH is especially important for GH-deficient females also at risk of precocious puberty. With higher doses of

cranial irradiation (>35 Gy), deficiencies in the gonadotropins can be seen, with a cumulative incidence of 10% to 20% at 5 to 10 years posttreatment [70].

Table 12 Neuroendocrine Late Effects

Late Effects	Causative Treatment	Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
GH deficiency	**Radiation:** >18 Gy to H-P axis	Falling off of growth curve, inadequate growth velocity, inadequate pubertal growth spurt	Annual stadiometer height (every 6 months at age 9-12 years), growth curve, bone age at 9 years, then every year to	GH therapy, delay puberty with gonadotropin releasing hormone (GnRH) agonist
Adrenocorticotropic hormone (ACTH) deficiency	**Radiation:** >40 Gy to H-P axis	Muscular weakness, anorexia, nausea, weight loss, dehydration, hypotension, abdominal pain, increased pigmentation (skin, buccal mucosa)	Cortisol (a.m.) baseline, prn symptoms (insulin–hypoglycemia; metapyrone stimulation tests)	Hydrocortisone
	Surgery: Tumor in region of H-P axis			
Thyrotropin-releasing hormone (TRH) deficiency	**Radiation:** >40 Gy H-P axis	Hoarseness, fatigue, weight gain, dry skin, cold intolerance, dry brittle hair, alopecia, constipation, lethargy,	Free T4, T3, TSH baseline, every 3-5 years	Hormone replacement with thyroxine,
Precocious puberty (especially females)	**Radiation:** >20 Gy to H-P axis	Early growth spurt, false catch-up, premature sexual maturation; female: breast development and pubic hair before 8 years and menses before 9 years; male: testicular/penile growth and pubic hair before 9-9.5 years	Height, growth curve every year, bone age every 2 years until mature, (LH, follicle-stimulating hormone [FSH], estradiol or testosterone)(pelvic ultrasound, GnRH-stimulation testing)	GnRH agonist
	Surgery: Tumor in region of H-P axis			
Gonadotropin deficiency:				

Late Effects	Causative Treatment	Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
Male	**Radiation:** >40 Gy to hypothalamic region	Delayed/ arrested/absent pubertal development: lack of or diminished pubic and axillary hair, penile and esticular enlargement, voice change, body odor, acne; testicular atrophy (softer and smaller); failure to impregnate	Tanner stage, LH, FSH, estradiol every 3-5 years, (GnRH testing)	Anticipatory guidance regarding symptoms of estrogen deficiency, hormone replacement, early intervention may prevent osteoporosis, and atherosclerosis
	Surgery: Tumor in region of hypothalamus			
Female	**Radiation:** >40 Gy to hypothalamic region	Delayed/ arrested/ absent pubertal development including: breasts, female escutcheon, female habitus, vaginal estrogen effect, body odor, acne; changes in duration, frequency, and character of menstruation (less cramping) estrogen deficiency: hot flashes, vaginal dryness, dyspareunia, low libido; infertility (if not on birth control pills)	Tanner stage, LH, FSH, estradiol every 3-5 years, GnRH-stimulation tests	Anticipatory guidance regarding symptoms of estrogen deficiency, hormone replacement, early intervention may prevent osteoporosis, and atherosclerosis
	Surgery: Tumor in region of hypothalamus			
	Surgery: Tumor in region of hypothalamus			
Metabolic syndrome	**Chemotherapy:** Steroids	Obesity, hypertension, hyperlipidemia, hyperglycemia, insulin resistance with hyperinsulinemias	Fasting lipids, glucose, insulin levels, body mass index (BMI) evaluation	Refer to endocrinology
	Radiation: Questionable ≥18 Gy (dose not well established)			

Musculoskeletal System

Bone and Body Composition

Chondroblasts and chondrocytes are affected by radiation therapy in growing children, which can result in soft tissue hypoplasia and diminution of bone growth. These effects are associated with the total and fractional radiation dose, and the inclusion of the epiphyses in the radiation field.[] Craniospinal radiation results in both abnormal GH secretion and effects on the vertebral bodies.[71]

Avascular necrosis has been reported in survivors of ALL who were treated by conventional therapy or by HSCT, with corticosteroids representing a significant risk factor [72]. In the closed CCG 1961 protocol, among 2,077 accrued patients, unifocal osteonecrosis was seen in 19 patients, and multifocal disease in 74 [73].

Bone mineral density in childhood cancer survivors may be reduced, especially in children treated for ALL, in whom it has been best studied. An increased incidence of fractures and osteonecrosis also occurs in these patients. Risk factors include increased age at time of exposure, estrogen deficiency, female gender, corticosteroid use and type, GH deficiency and cranial radiation [74].

Obesity

Abnormal body composition is also reported in excess in survivors of pediatric ALL. One study evaluated obesity in 1,764 ALL survivors followed in the CCSS, and compared them with a cohort of 2,565 siblings. The odds ratio for being obese was 2.6 for female survivors and 1.9 for male survivors who received doses of radiation greater than 20 Gy. The highest risk was for females treated at 4 years and younger with cranial radiation doses of greater than 20 Gy. Risk of obesity was not increased among ALL survivors treated with

chemotherapy alone or with doses of cranial radiation of 10 Gy to 19 Gy [75]. Genetic predisposition may be an important factor in risk for obesity in these ALL survivors. The CCSS has found higher BMI to be associated with a polymorphism in the leptin receptor gene [76]. A study from Denmark reports reduced lean body mass among survivors of childhood non-Hodgkin's lymphoma and Hodgkin's lymphoma [77]. Children treated for brain tumors are at risk for development of obesity because of hypothalamic dysfunction resulting from the tumor, surgery, or irradiation [78].

A number of endocrinologic and metabolic findings, including increased body mass index, can be summarized as the metabolic syndrome. This includes insulin resistance, hyperglycemia, hyperinsulinemia, hypertension, hyperlipidemia, and obesity. It is, at least in part, because of disturbances of the H-P axis,

Table 13 Musculoskeletal Late Effects

Late Effects	Causative Treatment	Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
Muscular hypoplasia	**Radiation:** >20 Gy (growing child); younger children more sensitive	Asymmetry of muscle mass when compared with untreated area, decreased range of motion, stiffness and pain in affected area	Careful comparison and measurement of irradiated and unirradiated areas, range of motion	Prevention: good exercise program, range of motion, muscle strengthening
	Surgery: Muscle loss or resection			
Spinal abnormalities: scoliosis, kyphosis, lordosis, decreased sitting height	**Radiation:** For young children, radiation therapy to hemiabdomen or spine (especially hemivertebral); 10 Gy (minimal effect), >20 Gy (clinically notable defect)	Back pain, hip pain, uneven shoulder height, rib humps or flares, deviation from vertical curve, gait abnormalities	Standing and sitting height at each visit and plot on chart (stadiometer), during puberty examine spine every 3-6 months until growth is completed and then every 1-2 years, spinal films baseline during puberty, then as needed for curvature (COBB technique to measure curvature)	Refer to orthopedist if any curvature is noted, especially during a period of rapid growth
	Surgery: Laminectomy			
Length discrepancy	**Radiation:** >20 Gy	Lower back pain, limp, hip pain, discrepancy in muscle mass and length when compared with untreated extremity, scoliosis	Annual measurement of treated and untreated limb radiograph baseline to assess remaining epiphyseal growth, radiographs annually during periods of rapid growth	Contralateral epiphysiodesis; limb-shortening procedures
Pathological fracture	**Radiation:** >40 Gy	Pain, edema, ecchymosis	Baseline radiograph of treated area to assess bone integrity, then as needed for symptoms	Surgical repair of fracture; may require internal fixation
	Surgery: Biopsy			
Osteonecrosis	**Chemotherapy:** Steroids	Pain in affected joint, limp	Radiograph, CT scan as needed for symptoms	Symptomatic care; joint replacement
	Radiation: >40-50 Gy (more common in adults)			

Osteopenia/ osteoporosis	**Chemotherapy:** Steroids	Fractures, pain	DEXA — intervals of testing unclear. Pediatric norms not well established. Best data are in adults	Calcium supplementation, increase weight bearing exercise; refer to endocrinology
	Radiation: >18 Gy cranial radiation therapy			

Reproductive System

Gonadal Function

Alkylating agents are the chemotherapeutic agents most responsible for gonadal toxicity.

Male Gonadal Function

Spermatogenesis is highly sensitive to cyclophosphamide, with a dose-effect exhibited that is exacerbated by coadministration of other alkylating agents, such as procarbazine [79]. With the common use of multiagent therapy that includes cyclophosphamide, sarcoma patients are also at increased risk of infertility, again with a dose response effect Review of the available studies has led to the consensus that males who receive less than 4 gm/m^2 of cyclophosphamide without any other alkylating agents and without either testicular or cranial radiation are likely to retain their fertility. Doses greater than 9 gm/m^2 are unlikely to result in any conservation of fertility [80].

The degree and permanency of radiation therapy-induced damage to the male reproductive system are dose, field and schedule, and age dependent. The germinal epithelium is damaged by much lower doses (<1 Gy) of radiation therapy than are Leydig cells (20 Gy-30 Gy) [81]. Although temporary oligospermia can occur after these very low radiation doses, permanent azoospermia results from higher doses of greater than 3 Gy to 4 Gy. The potential

for a return of spermatogenesis in the intermediate dose range of 1 Gy to 3 Gy is variable [81].

Female Gonadal Function

Unlike the situation in males, hormonal function and potential for fertility are synchronous in females. Prepubertal females possess their lifetime supply of oocytes, with no new oogonia formed after birth. Risks of menstrual irregularity, ovarian failure, and infertility increase with age at treatment [81]. A study of 2,498 survivors and 3,509 siblings treated between 1945 and 1975, found a 7% fertility deficit among female survivors as compared with their siblings. Forty-two percent of those with alkylating agent exposure and abdominal radiation experienced menopause by age 31 years [82].

The ovary is sensitive to the effects of ionizing radiation. Adverse ovarian effects vary depending on factors such as dose, schedule, and age. The younger the child, the larger the oocyte pool, and the later the menopause [81]. While radiation doses greater than 8 Gy are associated with ovarian ablation, lower doses may not cause infertility.[] Younger girls are more resistant than adolescents. Whole abdomen doses of 20 Gy to 30 Gy are associated with primary or premature secondary ovarian failureAbdominal radiation therapy at similar doses can lead to reduced uterine volume and decreased elasticity, increasing risk of spontaneous miscarriage, premature birth, and intrauterine growth retardation [82].

Table 14 Male Gonadal Late Effects

Late Effects	Causative Treatment	Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
Germ cell damage: oligospermia/ azoospermia	**Chemotherapy:** cyclophosphamide, mechlorethamine, lomustine (CCNU)/carmustine (BCNU), procarbazine, ifosfamide, busulfan, melphalan, dacarbazine (DTIC)	Testicular atrophy (softer and smaller), failure to impregnate	Tanner stage, inquire regarding previous sperm banking, determine testicular size and consistency, LH, FSH, testosterone: (1) for failure of pubertal development, (2) baseline when sexually mature, (3) for failure to impregnate (repeat every 3 years for possible recovery), analysis of sperm at maturity, or for failure to impregnate (repeat every 3-5 years to assess recovery)	Instruct on testicular self-examination, anticipatory guidance regarding germ-cell damage, referral to reproductive endocrinology, infertility counseling, and alternate strategies for fathering
	Radiation: >1-6 Gy			
	Surgery: Orchiectomy or surgical manipulation			
Leydig cell damage: testosterone deficiency	**Chemotherapy:** cyclophosphamide/etoposide	Delayed/ arrested/ absent pubertal development, pubic and axillary hair (female hair pattern), lack of penile and testicular enlargement, voice change, body odor and acne, testicular atrophy (softer and smaller)	LH and testosterone at age 13 years, failure of pubertal development; baseline, if sexually mature; changes in libido or sexual performance	Testosterone replacement and anticipatory guidance regarding testosterone deficiency
	Radiation: >24 Gy to the testes (direct or scattered from pelvis)			
	Surgery: Orchiectomy			

Table 15 Female Gonadal Late Effects

Late Effects	Causative Treatment	Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
Ovarian failure	**Chemotherapy:** mechlorethamine, cyclophosphamide, procarbazine, busulfan, melphalan, dacarbazine (DTIC), carmustine (BCNU), CCNU, ifosfamide	Delayed/ arrested/ absent pubertal development including: breasts, female escutcheon, female habitus, vaginal estrogen effect, development of body odor and acne, changes in duration, frequency, and character of menses (cramping), estrogen deficiency: hot flashes, vaginal dryness, dyspareunia, low libido, infertility	Tanner stage, LH, FSH, estradiol: (1) age 12 yrs, (2) failure of pubertal development, (3) baseline when fully mature, (4) as needed for symptoms, assess basal body temperature (midcycle elevation suggests ovulation), (dehydroepiandrosterone [DHEAs] for failure of development)	Hormone replacement (estrogen), anticipatory guidance regarding symptoms of estrogen deficiency and early menopause, referral to reproductive endocrinology, alternate strategies for parenting, early intervention (hormone replacement may prevent osteoporosis, atherosclerosis)
	Radiation: 4-12 Gy tolerance decreases with increasing age			
	Surgery: Oophorectomy or oophoropexy			
Vagina: fibrosis/diminished growth	**Chemotherapy:** actinomycin D and doxorubicin enhance radiation therapy effect)	Painful intercourse, vaginal bleeding, small vaginal vault	Pelvic exam (possibly under anesthesia) baseline, during puberty and as needed for symptoms	Dilations, reconstructive surgery, potential need for cesarean section
	Radiation: >40 Gy			
Uterus: fibrosis/decreased growth	**Radiation:** >20 Gy (prepubertal), >40-50 Gy (postpubertal)	Multiple spontaneous abortions, low birth-weight infants, small uterus	Pelvic: baseline, puberty, then annually	Questionable endometrial biopsy, counsel regarding pregnancy

Late Effects	Causative Treatment	Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
Ureter: fibrosis	**Radiation:** >50-60 Gy	Frequent urinary tract infections (UTIs), pelvic hypoplasia, hydronephrosis	Urinalysis every year (urethrogram)	UTI prophylaxis

Reproduction

With more childhood cancer survivors retaining their fertility, pregnancy outcome data are now available. In a study of 4,029 pregnancies among 1,915 women followed in the CCSS, there were 63% live births, 1% stillbirths, 15% miscarriages, 17% abortions, and 3% unknown or in gestation. Risk of miscarriage was 3.6-fold higher in women treated with craniospinal radiation and 1.7-fold higher in those treated with pelvic radiation. Chemotherapy exposure alone did not increase risk of miscarriage. Compared with siblings, survivors were less likely to have live births, more likely to have medical abortions, and more likely to have low-birth-weight babies [83].

Another study evaluated pregnancy outcomes of partners of male survivors. Among 4,106 sexually active males, 1,227 reported they sired 2,323 pregnancies, which resulted in 69% live births, 13% miscarriages, 13% abortions, and 5% unknown or in gestation at the time of analysis. Compared with partners of male siblings, there was decreased risk of live births (RR = 0.77), but no significant differences of pregnancy outcome by treatment [84].

In a report of 2,198 offspring of adult survivors treated for childhood cancer between 1945 and 1975 compared with 4,544 offspring of sibling controls, there were no differences in the proportion of offspring with cytogenetic syndromes, single-gene defects, or simple malformations. There was similarly no effect of type of childhood cancer treatment on the

occurrence of genetic disease in the offspring. A population-based study of 2,630 live-born offspring of childhood cancer survivors versus 5,504 live-born offspring of the survivors' siblings found no differences in proportion of abnormal karyotypes or incidence of Down syndrome or Turner syndrome between survivor and sibling offspring [85].

Second Malignant Neoplasms

Several large studies have examined the incidence and spectrum of second malignant neoplasms (SMNs) in childhood cancer survivors, in whom the cumulative risk at 20 years posttreatment varies from 3% to 10% and is 3 to 20 times greater than that expected in the general population. A number of treatment-related risk factors have been identified. Notably, radiation therapy is associated with the development of solid tumors as well as leukemia. Alkylating agents, platinums, and topoisomerase II inhibitors are associated with the development of leukemia [86] Epipodophyllotoxins are known to increase the risk for secondary leukemia, and anthracyclines may also increase this risk after treatment for solid tumors [87]. In an analysis of SMN in the Childhood Cancer Survival Study (CCSS), which excluded patients with retinoblastoma, the standardized incidence ratio (SIR) was 6.4, with a 20-year incidence of 3.2% and an absolute excess risk of 1.88 malignancies per 1,000 years of patient follow-up. Risk of SMN was elevated for all primary childhood cancer diagnoses, with the lowest SIR reported for non-Hodgkin’s lymphoma (3.2) and the highest for Hodgkin’s lymphoma (9.7). Risk was elevated for secondary leukemia, lymphoma, central nervous system tumors, soft tissue and bone sarcomas, melanoma, and breast and thyroid cancer, with the lowest SIR reported for lymphoma (1.5) and the higher SIRs reported for breast cancer (16.2) and bone sarcoma (19.1). In multivariate analyses adjusted for radiation exposures, SMNs were independently associated with female sex, younger age at diagnosis of childhood cancer, childhood cancer diagnosis of Hodgkin’s lymphoma, or soft tissue sarcoma and exposure to alkylating agents [88]. The CCSS has also reported an association between gene

polymorphisms in glutathione-S-transferase M1 (*GSTM1*), glutathione-S-transferase T1 (*GSTT1*), and *XRCC1,* and susceptibility to radiation therapy-related SMNs in childhood Hodgkin's lymphoma survivors [89]. The risk of leukemia appears to plateau at 10 to 15 years posttherapy, while the risk of second solid malignancies rises with ongoing follow-up, with a lifetime risk still unknown.[88].

Several studies have examined the risk of SMNs in survivors of Hodgkin's lymphoma, in whom the incidence of secondary breast and thyroid cancer is particularly high. Survivors of Hodgkin's lymphoma are also at increased risk of second leukemia, sarcoma, melanoma, and lung, thyroid, and gastrointestinal cancer.

Patients who undergo bone marrow transplantation have a risk of developing SMNs, especially solid tumors. This increased risk has been observed even 20 years posttransplant [90].

Patients may be at risk of SMNs by virtue of a cancer predisposition syndrome, which also placed them at risk for their primary cancer. This limited population should be targeted for education, counseling, and extraordinary surveillance because of their genetic predisposition to cancer.[25] This includes children with the genetic form of retinoblastoma. In these individuals, the SMN risk approaches 50% at 50 years from treatment if they received external-beam radiation therapy, and 25% at 50 years without previous radiation therapy treatment [91].

Breast cancer at an early age, sarcoma, and other cancers can be expected in children with Li-Fraumeni syndrome or Li-Fraumeni-like syndrome [92]. Since hepatoblastoma and fibromas have been associated with familial polyposis coli, children with those tumors should be examined for the polyposis gene (*APC*) and screened for colon cancer, as appropriate [93].

Monitoring for Late Effects in Childhood Cancer Survivors

The need for long-term follow-up for childhood cancer survivors is supported by the American Society of Pediatric Hematology/Oncology, the International Society of Pediatric Oncology, and the American Academy of Pediatrics. Survivors should seek care from professionals with expertise in the recognition and management of late effects [94]. Comprehensive monitoring guidelines for late effects have been developed within the Children's Oncology Group [95].

There is no evidence for the optimum setting for following up long term survivors.Adult cancer specialists who may lack the specific training required may not be appropriate to follow up childhood cancer survivors.Anticipaton and monitoring late adverse effects to optimize prevention and treatment outcomes requires multidisciplinary expertise, which should include one member as the key worker [6].

Table 16 Multidisciplinary follow up team

Adult Oncologist	Pediatric neurosurgeon
Clinical psychologist	Pediatric oncologist
General practitioner	Radiation oncologist
Pediatric endocrinologist	Social worker
Pediatric neurologist	Specialist nurse
Dentist	Optician

Table 17 Scottish guidelines for childhood cancer survivor follow up

Level	Treatment	Method of follow up	Frequency	Examples
1	Surgery alone Low risk	Postal or telephone	1-2 years	Wilms tumour stage I

	chemotherapy			
2	Chemotherapy Low dose cranial irradiation ≤ 24 Gy	Nurse or primary care-led	1-2 years	ALL in remission
3	Radiotherapy HDCT	Medically supervised follow up clinic	Annual	Brain tumours Post BMT

FOLLOW UP STRATERGIES

The degree and nature of long term morbidity risk will depend on the site of the underlying malignancy, the type and intensity of treatment and age at treatment. Three levels of follow up groups are described Table17 [6]

The St Jude model of Long term survivor care

The broad mission of the St Jude After Completion Therapy clinic (ACT) is to improve the quality of life of the long term childhood cancer survivor through annual assessment of the survivor's physical and emotional health, social functioning, and educational and vocational achievement. Patients who are in remission 5 years after diagnosis and 2 years after completion of neoplastic therapy are eligible for transfer to ACT clinic.

Table 18 After completion of therapy interventions to facilitate transition of survivor care [96] St Judes model

Nurse practitioner	Current health problems Reproductive status Psychosocial functioning Health related QOL
Social Worker	Marital status Academic /employment status Living arrangements] Maladaptive behaviour
Clinic Nurse	Education about breast /testicular self examination
Subspeciality provider	Consultant assessment as indicated
Physician	Review of ACT clinical summary Review and screening of cancer related health risks Advise for risk reducing behaviours

PATIENTS AND METHODS

PATIENTS AND METHODS

Inclusion criteria

- All subjects who were ≤ 14 years at the time of diagnosis of cancer
- Has completed 3 years of follow up after primary antineoplastic therapy
- Has completed 5 years of follow up after antineoplastic therapy for relapse

Exclusion criteria

- All subjects who were >14 years at the time of diagnosis of cancer
- Subjects who were < 14 years of diagnosis and has not completed 3 years of follow up
- Patients who are receiving antineoplastic therapy
- Patients who had a relapse of their primary malignancy and has not completed 5 years of follow up
- Survivors who were not willing to provide informed consent for enrolment to ACT clinic or neurocognitive assessment.

Subjects

A group of 155 consecutive long-term survivors of childhood cancer have been prospectively studied at the After Completion Therapy (ACT) clinic, medical oncology unit of the Cancer Institute (WIA), Chennai, India.

This included children diagnosed between 1968-2001.All subjects who were ≤ 14 years at the time of diagnosis and had completed 3 years follow up were included in the study.

Quality of life analysis was done in 56 subjects and neurocognitive assessment was done in 20 survivors of acute lymphoblastic leukemia after written informed consent.

Methods

Evaluation at the ACT clinic included complete history ,anthropometric measurements for each subject and a clinical examination with special emphasis on late toxicities and specific investigations to detect organ toxicities as shown in Table-19.Details of the type and doses of treatment received were noted.Semen analysis, thyroid hormonal evaluation and sex hormone evaluation was done in specific cases at risk.

Quality of life was assessed by Cancer Institute quality of life standardized questionnaire [97]. Dimensions for QOL included general well being, physical well being, psychological well being, interpersonal relationship, sexual and personal ability, cognitive well being, optimism and belief, economical well being, informational support, patient physician relations ship and body image. 56 childhood cancer survivors were analyzed for their QOL.

Neurocognitive assessment was done in 20 survivors of acute lymphoblastic leukemia using Malins Intelligence Scale for Indian children for subjects aged 6 years to 16 years [98].

Participants older than 16 years were administered the Wechsler Adult Intelligence Scale-Revised (WISA-R)[99]. Indian adaptation which constituted of 11 sub tests -information, comprehension, airthmetic, similarities, digit span, vocabulary (verbal scale) and digit symbol, picture completion, block design, picture arrangement, object assembly (performance scale)

Subjects were assessed for abstract thinking, reasoning, attention concentration,decision making and memory and was classified as per table20.

Table 19 WAIS –Intelligence Classification

WAIS – Score	Classification
≥130	Very superior
120-129	Superior
110-119	Bright normal
90-109	Average
80-89	Dull normal
70-79	Border line
≤69	Mental defective

The subjects were also provided counseling and education for healthy living and referred to sub specialists if specific toxicity was detected In subjects who underwent splenectomy specific counseling regarding the risk of severe infections was given.

STUDY PERIOD

May 2004 to May 2006

RESULTS

Of 155 subjects 114 subjects were males.19 subjects had a family history of cancer. Pattern of diagnosis was as noted in Table-21

Age distribution showed 90(58%) subjects belonged to the second decade as shown in Fig-1 Duration of follow up extended from 3 years to 37 years. Median duration of follow up was 8 years and majority (64%) was in the first decade of follow up. (Fig-3)

151(97%) subjects had received chemotherapy, 85(55%) subjects received radiotherapy, and 1 subject had high dose chemotherapy and PBSCT. 26 (17%)subjects underwent surgery out of which 3 had splenectomy 2 of them had hodgkins lymphoma and 1 acute lymphoblastic leukemia, 2 had enucleation and 4 had nephrectomy (Fig-2)

3(1.9%) of male subjects consumed alcohol and 1(0.6%)subject had history of smoking. None of the female subjects had history of smoking or alcohol consumption. Majority of patients had normal or low normal BMI ,26% and 68 % respectively. Pattern of late effects detected in the ACT clinic is noted in Table-22.

Male and female gonadal dysfunction was the most common late toxicity noted (25%). Commonest male gonadal dysfunction was oligospemia and azzospermia (89 %) while the most common female gonadal dysfunction was amennorhea or oligomenorrhea (78%). All the subjects had received combination chemotherapy which included alkylating agents. (fig-5)

7 subjects had not attained height for age and 4 of them had received prophylactic cranial irradiation. Hypothyroidism was noted in 4of 23 subjects tested for thyroid dysfunction. This included 2subject who had Hodgkins lymphoma ,1 subject had Non hodgkins lymphoma and 1 subject was a survivor of acute lymphoblastic leukemia.All subjects had received

radiotherapy to head and neck.3 subjects had thyroid profile suggestive of subclinical hypothyroidism.

Two second malignant neoplasms were observed among the 155 subjects.

1 year old female child diagnosed to have bilateral retinoblastoma in 1968 and treated with external beam radiotherapy 5000cGY presented in February 2005 with a preauricular swelling and lymphadenopathy and was diagnosed as ectomesenchymoma of parotid gland.

8 year old boy diagnosed as Hodgkin's lymphoma stage II A in 1973 underwent staging laprotomy and treated with combination chemotherapy and mantle field of radiotherapy presented in May 2005 with dysphagia and was diagnosed to have carcinoma hypopharynx.

Two of the subjects were detected to have cardiovascular dysfunction.17 year old male survivor diagnosed as lymphoblastic lymphoma in 1995 and had received anthracycline based chemotherapy and irradiation to the mediastinum was detected to have dilated cardiomyopathy with congestive cardiac failure.The other subject was a 24 year old male survivor of Hodgkin lymohoma who had received subtotal lymph nodal irradiation and was on 16th year of follow. He was asymptomatic and incidentally detected to have mitral valvular regurgitation.

Post mantle field radiotherapy lymphedema was noted in one subject. One of the subject who is a survivor of ALL had developed avascular necrosis of the head of femur. Two of the subjects were noted to have gynaecomstia.

No evidence of cataract was noted among the survivors.

Quality of life assessment showed high QOL in 31(55.3%) subjects and average QOL in 21 subjects. (37.5%)

Neurocognitive assessment was done in 20 survivors of acute lymphoblastic leukemia. All the survivors had received prophylactic cranial RT (median dose 20 Gy) and 12 doses of intrathecal methotrexate as per MCP 841 protocol. The mean age of children in the combined group was 17.3 years**.** Males constituted 93% of the study group. Socioeconomic status (SES) was not consistent. Median duration of follow up was 9.3 years. 3 (15%)of the subjects had WISA- R score suggestive of mentally deficient IQ(score≤ 69) while 12 (60)% had average IQ. (score 90-109).

Table21 Pattern of diagnosis among survivors

Diagnosis	Number
Acute Lymphoblastic leukemia	50
Hogkins lymphoma	55
Non hodgkins lymphoma	21
Osteosarcoma/soft tissue sarcoma	12
Germ cell tumours	4
Wilms tumour	5
Retinoblastoma	2
Acute myeloid leukemia	2
Others	4

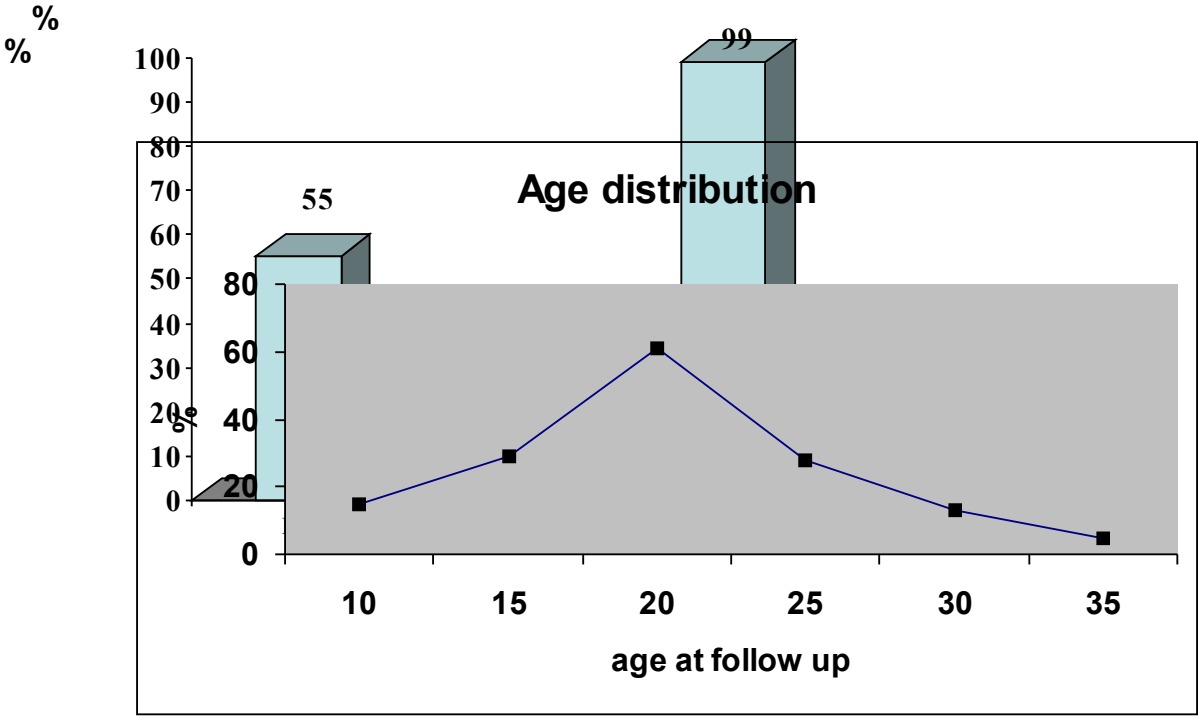
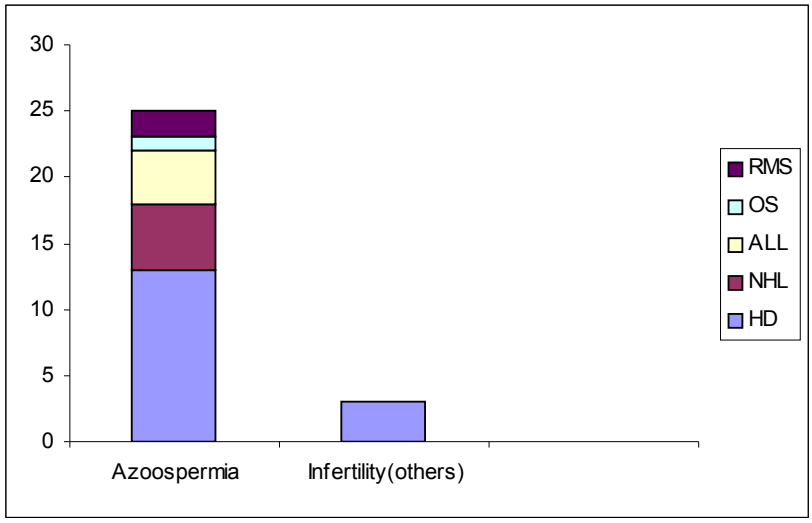


Fig 1 - age of survivors on follow up at the ACT clinic

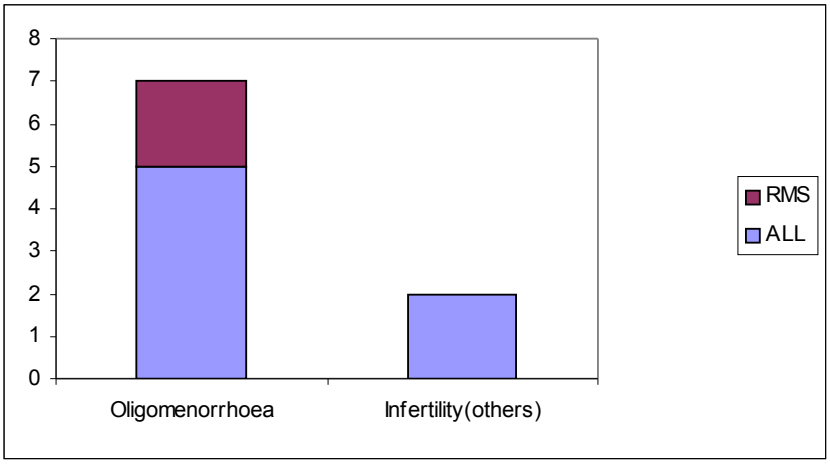
Fig-2 Pattern of modality of treatment received among survivors

Fig. 3 Body mass index pattern among childhood cancer survivors

Fig-4 Duration of follow up in years among survivors (N=155)



MALE (N=28)



FEMALE (N=09)

Fig-5 Pattern of gonadal dysfunction among survivors

Abbreviation

RMS-rhabdomyosarcoma,NHL-non hodkins lymphoma, ALL-acute lymphoblastic leukemia , HD – hodgkins lymphoma

Fig-6Long Term Survivor of Hodgkins Lymphoma with gynaecomazia and neck muscle wasting

Fig-4Post Mantle irradiation Lymphedema

Table 22 Pattern of late effects noted in ACT Clinic

Pattern of late effects	Number of subjects
Under nutrition	9(6%)
Obesity	3(1.9%)
Impaired male gonadal dysfunction	28(25%)
Impaired female gonadal dysfunction	9(22%)
Seroconversion to HBV	41(26.4%)
Seroconversion to HCV	38(24.5%)
Both HBV and HCV	18(11.6%)
Hypothyroidism	4(17.3%)
Subclinical hypothyroidism	3(13%)
Second neoplasm	2(1.3%)
Muskuloskeltal	12(8%)
Lymphedema	1(0.6%)
Impaired growth pattern	7(5%)
Cardiovascular dysfunction	2(1.3%)
Dental abnormalities	25(16.1%)

DISCUSSION

DISCUSSION

The results of our study show that the commonest long term sequalae of therapy was impaired reproduction capacity and impaired growth pattern. Obesity was not common and majority of the survivors had good quality of life. Limitations of our study included the study population did not involve all the long term survivors and included only the survivors who agreed to attend the ACT clinic and hormonal evaluation was not carried out in all subjects as is the standard in other ACT clinics due to economic considerations.

Severe obesity was noted in 3 of subjects of whom only 1 subject had received cranial irradiation. Majority of our patients had a lower BMI and obesity was not common as compared to western data Obesity is reported in excess in survivors of pediatric ALL. The highest risk in a study conducted in the United States was for females treated at 4 years and younger with cranial radiation doses of greater than 20 Gy [75].

Although growth hormone estimation was not done in our study ,7% of our subjects had not attained the height for age and 4 of the subjects had received cranial irradiation. Growth hormone (GH) deficiency, delayed or precocious puberty, and hypopituitarism can occur in childhood cancer survivors; hypothalamic dysfunction being the most common abnormality noted after cranial irradiation [65]. A study conducted in North America in118 ALL survivors treated with 24 Gy cranial irradiation, showed 74% had impaired growth pattern due to growth hormone deficiency [68].

Impaired reproduction capacity was the commonest long term toxicity noted in our study All our subjects who had gonadal dysfunction received alkylating agents.

Alkylating agents, widely used in childhood cancer therapy are the chemotherapeutic agents most responsible for gonadal toxicity. Spermatogenesis is highly sensitive to cyclophosphamide, with a dose-effect exhibited that is exacerbated by coadministration of other alkylating agents, such as procarbazine [79]. Furthermore permanent azoospermia results from radiation doses of greater than 3 Gy to 4 Gy [79]. In females risks of menstrual irregularity, ovarian failure, and infertility increase with age at treatment. A Canadian study of female childhood cancer survivors, have shown increased incidence of infertility and early menopause [100] .

Seroconversion rate to HBSAg and HCV was 26% and 25 % compared to a western prospective study where the conversion rates were 16% and 3.2% [102]. Improved screening for donors has reduced the seroconversion rates in the recent times. This subset of survivors may require more close monitoring as they are more at risk of developing cirrhosis and hepatocellular carcinoma None of these subjects had features of cirrhosis or portal hypertension on sonographic study 16 % of subjects who had dental caries were provided dental consultation and appropriate treatment was given Salivary gland irradiation incidental to treatment of head and neck malignancies or Hodgkin's lymphoma causes a qualitative and quantitative change in salivary flow that can result in the development of dental caries[NCI82].

Hypothyridism was noted in 4 of 23subjects in our study. All the subjects had received radiation therapy to head and neck. Subclinical hypothyroidism was noted in 3 survivors. Incidence of thyroid dysfunction differ depending on the dose of radiation, the length of follow-up, and the biochemical criteria utilized to make the diagnosis [103]. Screening for thyroid function was done only in subjects who were susceptible to hormonal dysfunction

Both cases in this study had received irradiation and second neoplasm developed within

or adjacent to the field of irradiation. Irradiated survivors had a higher cumulative incidence of developing a second neoplasm than nonirradiated survivors in St Judes study [104]. In a recent CCS study it was noted that the risk of developing second malignancy was significantly elevated following all childhood cancer diagnosed except CNS neoplasm and was highest following neuroblastoma and soft tissue sarcoma [105].

3 of subjects had splenectomy. Splenectomy increases risk of life-threatening invasive bacterial infection [42]. However in this study no severe or life threatening infections were noted. Two of our survivors with retinoblastoma had undergone enucleation . For survivors of retinoblastoma, a small orbital volume may result from either enucleation or radiation therapy. Age younger than 1 year may increase risk, but this is not consistent across studies. Better management of prosthetic implants and newer methods of delivering radiation therapy are likely to reduce risk[106].. None of our subjects had developed cataract.

Our study showed average and good quality of life in 93 % of survivors with standardized questionnaire although our sample size was small. In a recent series from India, severe psychological problems were encountered in 12 % of survivors. [29].As a group, childhood cancer survivors appear to be within the normally expected range in terms of psychosocial adjustment. Additionally a subset had psychological difficulties that resulted in functional impairment [107]

Although baseline neurocognitive assessment was not done our study showed significant neurocognitive dysfunction with poor academic performance in 3 of 20 survivors of acute lymphoblastic leukemia. This is consistent with previous cross sectional studie[21]

Neurocognitive sequalae in childhood cancer are mainly due to the result of radiation to the whole brain or due to intrathecal or high dose methotrexate or cytarabine. Risk factors

include increasing radiation dose ,young age at the time of treatment, combined chemo radiotherapy and female gender.[NCI21] Deficits in fine motor skills, visual-spatial abilities, verbal and nonverbal memory, psychomotor speed and shifting of attention, auditory perception, word fluency, contingency naming, and the ability to follow directions have all been reported [7]

CONCLUSION

Conclusion

Long term morbidity risks in childhood cancer survivors largely relate to treatment modality and the challenge remains to improve survival rates whilst reducing the incidence and severity of treatment related late effects and to achieve optimal quality of life.

1) This study showed impaired reproduction capacity as the commonest long term sequalae with less incidence of obesity and a good quality of life among childhood cancer survivors

2) Future studies may include more active recruitment of subjects to improve the attendance in ACT clinic.

3) Monitoring for late effects help the oncologist or the physician in making an early diagnosis and to make corrective interventions and also help to develop more safer treatment modalities and there by improve the quality of life of long term survivors

4) The information provided by this ongoing study may allow clinicians to better monitor childhood cancer survivors in countries with limited resources.

BIBLIOGRAPHY

1. Ries LA, Smith MA, Gurney JG, et al., eds.: Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. Bethesda, Md: National Cancer Institute, SEER Program, 1999.

2. Shanta MA, Gajalakshmi CK, Swaminatham R. India, Madras Metropolitan Tumour Registry, 1982-1992. In *International Incidence of Childhood Cancer*, vol. II, IARC Scientific Publications no. 144, ed. Parkin DM, Kramárová E, Draper GJ, et al., 169-171. Lyon: International Agency for Research on Cancer1998.

3. Chandra A, Sagar T G, Swaminathan R:Childhood Cancer Epidemiology among Asian population in Indian sub-continent. A single institutional study from a Developing country".Ann Oncol; iii,148 ,2004 (Abstract).

4. Oeffinger KC, Hudson MM: Long-term complications following childhood and adolescent cancer: foundations for providing risk-based health care for survivors. CA Cancer J Clin 54 (4): 208-36, 2004

5. Schwartz CL: Long-term survivors of childhood cancer: the late effects of therapy. Oncologist 4 (1): 45-54, 1999

6. Long term follow up of childhood cancer : A national clinical guideline,Scottish Intercollegiate Guidelines Network, www.sign.ac.uk

7. Chandra A , Sagar T G Patterns of care and survival for children with cancer in a country with limited resources . Report from Regional Cancer Centre in India". . Accepted for publication in Annals of Oncology , 2006 issue.

8. Hewitt M, Weiner SL, Simone JV. Childhood cancer survivorship: improving care and quality of life: Institute of Medicine. Washington DC: The National Academy Press; 2003

9. Mertens AC,Yelugai V Potter J D et al: Late mortality experience in five year survivors of childhood cancer:Childhood Cancer Survivor Study J Clin Oncol;19(13): 3163-72. 2001

10. Curry HL, Parkes SE, Powell JE, Mann JR. Eur J Cancer. Mar; 42(4):501-8. 2006

11. Bhatia S, Landier W, Robison L: Late Effects of Childhood Cancer Therapy: Progress in Oncology Ch10: 171-199,2002

12. Duffner PK, Cohen ME: Long-term consequences of CNS treatment for childhood cancer, Part II: Clinical consequences. Pediatr Neurol 7 (4): 237-42,1991

13. Meadows AT, Gordon J, Massari DJ, et al.: Declines in IQ scores and cognitive dysfunctions in children with acute lymphocytic leukaemia treated with cranial irradiation.

Lancet 2 (8254):,1015-8,1981

14. Silber JH, Radcliffe J, Peckham V, et al.: Whole-brain irradiation and decline in intelligence: the influence of dose and age on IQ score. J Clin Oncol 10 (9):.1390-6, 1992

15. K. T., Yanofsky, R., Ludwig, R. N., Hill, D. E., Hart, B. L., Astur, R. S., & Snyder, T.). Hypoplasia of the cerebellar vermis and cognitive deficits in survivors of childhood leukemia. *Archives of Neurology, 51*, 985-993,1994

16. D. R., Moore, B. D., Francis, D. J., Jaffe, D. J., & Culbert, S. J.,). Neuropsychologic effects of chemotherapy on children with cancer: A longitudinal study. *Journal of Clinical Oncology, 14*, 2826-2835, 1996

17. P., Ungerer, J. A., Crawford, J. A., & Stevens, M. M. Cognitive effects of childhood leukemia therapy: A case for four specific deficits. *Journal of Pediatric Psychology, 16*(4), 475-488,1991.

18. B. D., Francis, D. J., Jaffe, D. J., & Culbert, S. J., Neuropsychologic effects of chemotherapy on children with cancer: A longitudinal study. *Journal of Clinical Oncology, 14*, 2826-2835, 1996.

19. U., Boodoo, G., Bouchard, T. J., Jr., Boytin, A. W.,et al. Intelligence: Knowns and unknowns. *American Psychologist, 51*(2), 77-101,1996.

20. Brown RT, Madan-Swain A, Pais R, et al.: Chemotherapy for acute lymphocytic leukemia: cognitive and academic sequelae. J Pediatr 121 (6): 885-9, 1992

21. Butler RW, Hill JM, Steinherz PG, et al.: Neuropsychologic effects of cranial irradiation, intrathecal methotrexate, and systemic methotrexate in childhood cancer. J Clin Oncol 12 (12): 2621-9, 1994

22. Kaleita TA, Reaman GH, MacLean WE, et al.: Neurodevelopmental outcome of infants with acute lymphoblastic leukemia: a Children's Cancer Group report. Cancer 85 (8):, 1859-65,1999

23. Waber DP, Tarbell NJ, Fairclough D, et al.: Cognitive sequelae of treatment in childhood acute lymphoblastic leukemia: cranial radiation requires an accomplice. J Clin Oncol 13 (10):, 2490-6, 1995

24. Fuemmeler BF, Elkin TD, Mullins LL: Survivors of childhood brain tumors: behavioral, emotional, and social adjustment. Clin Psychol Rev 22 (4):.547-85,2002

25. Zeltzer LK: Cancer in adolescents and young adults psychosocial aspects. Long-term survivors. Cancer 71 (10 Suppl): 3463-8, 1993

26. American Psychiatric Association.: Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. 4th ed. Washington, DC: American Psychiatric Association, 1994

27. Hobbie WL, Stuber M, Meeske K, et al.: Symptoms of posttraumatic stress in young adult survivors of childhood cancer. J Clin Oncol 18 (24): 4060-6, 2000

28. Recklitis C, O'Leary T, Diller L: Utility of routine psychological screening in the childhood cancer survivor clinic. J Clin Oncol 21 (5): 787-92, 2003.

29. Savita S G, Kurkre P, Arora B et al : Effectiveness of Psychological assessment and interventions in coping and care of long term survivors of childhood cancer in India; UICC world Cancer Progress Conference Proceedings2006

30. Schell MJ, McHaney VA, Green AA, et al.: Hearing loss in children and young adults receiving cisplatin with or without prior cranial irradiation. J Clin Oncol 7 (6): 754-60, 1989

31. Raney RB, Asmar L, Vassilopoulou-Sellin R, et al.: Late complications of therapy in 213 children with localized, nonorbital soft-tissue sarcoma of the head and neck: A descriptive report from the Intergroup Rhabdomyosarcoma Studies (IRS)-II and - III. IRS Group of the Children's Cancer Group and the Pediatric Oncology Group. Med Pediatr Oncol 33 (4): 362-71, 1999

32. Peylan-Ramu N, Bin-Nun A, Skleir-Levy M, et al.: Orbital growth retardation in retinoblastoma survivors: work in progress. Med Pediatr Oncol 37 (5): 465-70, 2001

33. Oberlin O, Rey A, Anderson J, et al.: Treatment of orbital rhabdomyosarcoma: survival and late effects of treatment--results of an international workshop. J Clin Oncol 19 (1): 197-204, 2001.

34. Van Kempen-Harteveld ML, Struikmans H, Kal HB, et al.: Cataract after total body irradiation and bone marrow transplantation: degree of visual impairment. Int J Radiat Oncol Biol Phys 52 (5): 1375-80, 2002

35. Maguire A, Craft AW, Evans RG, et al.: The long-term effects of treatment on the dental condition of children surviving malignant disease. Cancer 60 (10): 2570-5, 1987.

36. Kaste SC, Hopkins KP, Jones D, et al.: Dental abnormalities in children treated for acute lymphoblastic leukemia. Leukemia 11 (6): 792-6, 1997

37. Makkonen TA, Nordman E: Estimation of long-term salivary gland damage induced by radiotherapy. Acta Oncol 26 (4): 307-12, 1987

38. Dawson LA, Ten Haken RK, Lawrence TS: Partial irradiation of the liver. Semin Radiat Oncol 11 (3): 240-6, 2001

39. Strickland DK, Jenkins JJ, Hudson MM: Hepatitis C infection and hepatocellular carcinoma after treatment of childhood cancer. J Pediatr Hematol Oncol 23 (8): 527-9, 2001

40. Sher ME, Bauer J: Radiation-induced enteropathy. Am J Gastroenterol 85 (2): 121-8, 1990.

41. Emami B, Lyman J, Brown A, et al.: Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 21 (1): 109-22, 1991

42. Pickering LK, Peter G, Baker CJ, eds.: 2000 Red Book: Report of the Committee on Infectious Diseases. 25th ed. Elk Grove Village, Ill: American Academy of Pediatrics, 2000

43. Jockovich M, Mendenhall NP, Sombeck MD, et al.: Long-term complications of laparotomy in Hodgkin's disease. Ann Surg 219 (6): 615-21; discussion 621-4, 1994.

44. Coleman CN, McDougall IR, Dailey MO, et al.: Functional hyposplenia after splenic irradiation for Hodgkin's disease. Ann Intern Med 96 (1): 44-7, 1982.

45. Waghorn DJ, Mayon-White RT: A study of 42 episodes of overwhelming post-splenectomy infection: is current guidance for asplenic individuals being followed? J Infect 35 (3): 289-94, 1997

46. Hancock SL, Tucker MA, Hoppe RT: Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. JAMA 270 (16): 1949-55, 1993.

47. Hancock SL, Donaldson SS, Hoppe RT: Cardiac disease following treatment of Hodgkin's disease in children and adolescents. J Clin Oncol 11 (7): 1208-15, 1993.

48. Green DM, Grigoriev YA, Nan B, et al.: Congestive heart failure after treatment for Wilms' tumor: a report from the National Wilms' Tumor Study group. J Clin Oncol 19 (7): 1926-34, 2001

49. Shapira J, Gotfried M, Lishner M, et al.: Reduced cardiotoxicity of doxorubicin by a 6-hour infusion regimen. A prospective randomized evaluation. Cancer 65 (4): 870-3, 1990

50. Lipshultz SE, Giantris AL, Lipsitz SR, et al.: Doxorubicin administration by continuous infusion is not cardioprotective: the Dana-Farber 91-01 Acute Lymphoblastic Leukemia protocol. J Clin Oncol 20 (6): 1677-82, 2002

51. Adams MJ, Lipsitz SR, Colan SD, et al.: Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin Oncol 22 (15): 3139-48, 2004.

52. Schwartz CL, Hobbie WL, Truesdell S, et al.: Corrected QT interval prolongation in anthracycline-treated survivors of childhood cancer. J Clin Oncol 11 (10): 1906-10, 1993

53. Jakacki RI, Larsen RL, Barber G, et al.: Comparison of cardiac function tests after anthracycline therapy in childhood. Implications for screening. Cancer 72 (9): 2739-45, 1993

54. Kreisman H, Wolkove N: Pulmonary toxicity of antineoplastic therapy. Semin Oncol 19 (5): 508-20, 1992

55. Marina NM, Greenwald CA, Fairclough DL, et al.: Serial pulmonary function studies in children treated for newly diagnosed Hodgkin's disease with mantle radiotherapy plus

cycles of cyclophosphamide, vincristine, and procarbazine alternating with cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine. Cancer 75 (7): 1706-11, 1995

56. Nysom K, Holm K, Hertz H, et al.: Risk factors for reduced pulmonary function after malignant lymphoma in childhood. Med Pediatr Oncol 30 (4): 240-8, 1998

57. Leiper AD: Non-endocrine late complications of bone marrow transplantation in childhood: part II. Br J Haematol 118 (1): 23-43, 2002

58. Mertens AC, Yasui Y, Liu Y, et al.: Pulmonary complications in survivors of childhood and adolescent cancer. A report from the Childhood Cancer Survivor Study. Cancer 95 (11): 2431-41, 2002

59. Arndt C, Morgenstern B, Hawkins D, et al.: Renal function following combination chemotherapy with ifosfamide and cisplatin in patients with osteogenic sarcoma. Med Pediatr Oncol 32 (2): 93-6, 1999

60. Cassady JR: Clinical radiation nephropathy. Int J Radiat Oncol Biol Phys 31 (5): 1249-56, 1995

61. Ritchey ML, Green DM, Thomas PR, et al.: Renal failure in Wilms' tumor patients: a report from the National Wilms' Tumor Study Group. Med Pediatr Oncol 26 (2): 75-80, 1996.

62. Hancock SL, McDougall IR, Constine LS: Thyroid abnormalities after therapeutic external radiation. Int J Radiat Oncol Biol Phys 31 (5): 1165-70, 1995

63. Hancock SL, Cox RS, McDougall IR: Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med 325 (9): 599-605, 1991.

64. Constine LS, Donaldson SS, McDougall IR, et al.: Thyroid dysfunction after radiotherapy in children with Hodgkin's disease. Cancer 53 (4): 878-83, 1984

65. Gurney JG, Kadan-Lottick NS, Packer RJ, et al.: Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. Cancer 97 (3): 663-73, 2003

66. Merchant TE, Goloubeva O, Pritchard DL, et al.: Radiation dose-volume effects on growth hormone secretion. Int J Radiat Oncol Biol Phys 52 (5): 1264-70, 2002

67. Sklar C, Mertens A, Walter A, et al.: Final height after treatment for childhood acute lymphoblastic leukemia: comparison of no cranial irradiation with 1800 and 2400 centigrays of cranial irradiation. J Pediatr 123 (1): 59-64, 1993.

68. Schriock EA, Schell MJ, Carter M, et al.: Abnormal growth patterns and adult short stature

in 115 long-term survivors of childhood leukemia. J Clin Oncol 9 (3): 400-5, 1991.

69. Didcock E, Davies HA, Didi M, et al.: Pubertal growth in young adult survivors of childhood leukemia. J Clin Oncol 13 (10): 2503-7, 1995

70. Rappaport R, Brauner R, Czernichow P, et al.: Effect of hypothalamic and pituitary irradiation on pubertal development in children with cranial tumors. J Clin Endocrinol Metab 54 (6): 1164-8, 1982

71. Silber JH, Littman PS, Meadows AT: Stature loss following skeletal irradiation for childhood cancer. J Clin Oncol 8 (2): 304-12, 1990

72. Hoelzer D, Gökbuget N, Ottmann O, et al.: Acute lymphoblastic leukemia. Hematology (Am Soc Hematol Educ Program) : 162-92, 2002

73. Seibel NL, Steinherz P, Sather H, et al.: Early treatment intensification improves outcome in children and adolescents with acute lymphoblastic leukemia (ALL) presenting with unfavorable features who show a rapid early response (RER) to induction chemotherapy: a report of CCG-1961] Blood 102 (11): A-787, 2003.

74. Kaste SC, Jones-Wallace D, Rose SR, et al.: Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: frequency of occurrence and risk factors for their development. Leukemia 15 (5): 728-34, 2001

75. Oeffinger KC, Mertens AC, Sklar CA, et al.: Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. J Clin Oncol 21 (7): 1359-65, 2003

76. Ross JA, Oeffinger KC, Davies SM, et al.: Genetic variation in the leptin receptor gene and obesity in survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. J Clin Oncol 22 (17): 3558-62, 2004.

77. Nysom K, Holm K, Michaelsen KF, et al.: Degree of fatness after treatment of malignant lymphoma in childhood. Med Pediatr Oncol 40 (4): 239-43, 2003. [PUBMED Abstract]

78. Lustig RH, Post SR, Srivannaboon K, et al.: Risk factors for the development of obesity in children surviving brain tumors. J Clin Endocrinol Metab 88 (2): 611-6, 2003

79. Ben Arush MW, Solt I, Lightman A, et al.: Male gonadal function in survivors of childhood Hodgkin and non-Hodgkin lymphoma. Pediatr Hematol Oncol 17 (3): 239-45, 2000

80. Meistrich ML, Wilson G, Brown BW, et al.: Impact of cyclophosphamide on long-term reduction in sperm count in men treated with combination chemotherapy for Ewing and soft tissue sarcomas. Cancer 70 (11): 2703-12, 1992

81. Thomson AB, Critchley HO, Kelnar CJ, et al.: Late reproductive sequelae following treatment of childhood cancer and options for fertility preservation. Best Pract Res Clin

Endocrinol Metab 16 (2): 311-34, 2002

82. Byrne J, Mulvihill JJ, Myers MH, et al.: Effects of treatment on fertility in long-term survivors of childhood or adolescent cancer. N Engl J Med 317 (21): 1315-21, 1987

83. Green DM, Whitton JA, Stovall M, et al.: Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Am J Obstet Gynecol 187 (4): 1070-80, 2002

84. Green DM, Whitton JA, Stovall M, et al.: Pregnancy outcome of partners of male survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol 21 (4): 716-21, 2003

85. Winther JF, Boice JD Jr, Mulvihill JJ, et al.: Chromosomal abnormalities among offspring of childhood-cancer survivors in Denmark: a population-based study. Am J Hum Genet 74 (6): 1282-5, 2004

86. Metayer C, Lynch CF, Clarke EA, et al.: Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. J Clin Oncol 18 (12): 2435-43, 2000

87. Le Deley MC, Leblanc T, Shamsaldin A, et al.: Risk of secondary leukemia after a solid tumor in childhood according to the dose of epipodophyllotoxins and anthracyclines: a case-control study by the Société Française d'Oncologie Pédiatrique. J Clin Oncol 21 (6): 1074-81, 2003

88. Neglia JP, Friedman DL, Yasui Y, et al.: Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. J Natl Cancer Inst 93 (8): 618-29, 2001.

89. Mertens AC, Mitby PA, Radloff G, et al.: XRCC1 and glutathione-S-transferase gene polymorphisms and susceptibility to radiotherapy-related malignancies in survivors of Hodgkin disease. Cancer 101 (6): 1463-72, 2004

90. Baker KS, DeFor TE, Burns LJ, et al.: New malignancies after blood or marrow stem-cell transplantation in children and adults: incidence and risk factors. J Clin Oncol 21 (7): 1352-8, 2003

91. Wong FL, Boice JD Jr, Abramson DH, et al.: Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA 278 (15): 1262-7, 1997.

92. Malkin D, Jolly KW, Barbier N, et al.: Germline mutations of the p53 tumor-suppressor gene in children and young adults with second malignant neoplasms. N Engl J Med 326 (20): 1309-15, 1992

93. Garber JE, Li FP, Kingston JE, et al.: Hepatoblastoma and familial adenomatous polyposis. J Natl Cancer Inst 80 (20): 1626-8, 1988

94. Harvey J, Hobbie WL, Shaw S, et al.: Providing quality care in childhood cancer survivorship: learning from the past, looking to the future. J Pediatr Oncol Nurs 16 (3): 117-25, 1999.

95. Children's Oncology Group.: Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. Version 1.2, March 2004. Available online. Last accessed June 12, 2006.

96. Hudson et al : Monitoring Late Effects after Childhood Cancer ; Journal of Pediatric Oncology Nursing 21(3);1-5,2004.

97. Vidhubala et al : Validation of quality of life questionnaire for cancer patients –Indian scenario.Indian Journal of Cancer 42(3) 124-29,2005.

98. Malin AJ : Malin's Intelligence scale for Indian children ;Indian psychological corporation,1966.

99. Prabha R : Wechler,s adult performance intelligence scale-Indian adapatation,(form PR) Manasayan 1974.

Sklar CA, Robison LL, Nesbit ME, et al.: Effects of radiation on testicular function in long-term survivors of childhood acute lymphoblastic leukemia: a report from the Children Cancer Study Group. J Clin Oncol 8 (12): 1981-7, 1990.

100. Chiarelli AM, Marrett LD, Darlington G: Early menopause and infertility in females after treatment for childhood cancer diagnosed in 1964-1988 in Ontario, Canada. Am J Epidemiol 150 (3): 245-54, 1999

101. Segal BH: Infections in the Cancer Patient, in Devita VT 7th Ed:Priciples and Practice of Oncology,2477-2484.

102. Gleeson HK, Darzy K, Shalet SM: Late endocrine, metabolic and skeletal sequelae following treatment of childhood cancer. Best Pract Res Clin Endocrinol Metab 16 (2): 335-48, 2002.

103. Neugut AI: Second Cancers Among Long-Term Survivors of Cancer,ASCO 2004 Educational Book, 664-668, 2004.

104. Bassal M,Mertens AC,Taylor L et al:Risk of selected subsequent carcinomas in survivors of childhood cancer : A report from the Childhood cancer survivor study. J Clin Oncol 24(3): 476-83, 2006.

105. Kaste SC, Chen G, Fontanesi J, et al.: Orbital development in long-term survivors of retinoblastoma. J Clin Oncol 15 (3): 1183-9, 1997.

106. Gray RE, Doan BD, Shermer P, et al.: Psychologic adaptation of survivors of childhood cancer. Cancer 70 (11): 2713-21, 1992.